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(54) Title: 3-HETEROCYCLYLPROPANOHYDROXAMIC ACID AS PROCOLLAGEN C-PROTEINASE INHIBITORS

(57) Abstract: Compounds of compounds of formula (I) and their salts, solvates and prodrugs, wherein the substituents are as defined herein, are Procollagen C-proteinase inhibitors for the treatment of scars.



WO 02/079200 A1

## 3--HETEROCYCLYLPROpanOHYDROXAMIC ACID AS PROCOLLAGEN C-PROTEINASE INHIBITORS

This invention relates to a certain class of compounds, and the pharmaceutically acceptable salts, solvates and prodrugs thereof, which inhibit Procollagen C-proteinase ("PCP"). They are therefore useful in the treatment of mammals having conditions alleviable by inhibition of PCP. Especially of interest is an antiscarring treatment for wounds.

Fibrotic tissues, including dermal scars, are characterised by excessive accumulation of extracellular matrix, mainly collagen type I. It is thought that inhibition of collagen deposition will reduce formation of scar tissue. Collagen is secreted as the precursor, procollagen, which is transformed into the insoluble collagen by cleavage of the C-terminal propeptide by PCP. PCP is a zinc-dependent metalloprotease which is secreted from TGF- $\beta$ -activated fibroblasts belonging to the subfamily of astacin-like proteases and able to cleave the C-terminal peptide of types I, II and III procollagens. Furthermore, data suggest that PCP activates lysyl oxidase, an enzyme essential for the formation of covalent cross-links which stabilise the fibrous form of collagen. Therefore, inhibition of PCP may not only reduce collagen deposition but may also make collagen more accessible for degradation.

Collagen is integral to, among other things, the proper formation of connective tissue. Thus, the over- or under-production of collagen or the production of abnormal collagen (including incorrectly processed collagen) has been linked with numerous connective tissue diseases and disorders. Mounting evidence suggests that PCP is an essential key enzyme for the proper maturation of collagen (see for example International Patent Application publication number WO 97/05865).

The present invention relates to substances capable of inhibiting PCP activity in order to regulate, modulate and/or reduce collagen formation and deposition. More specifically, the invention relates to the use of compounds and pharmaceutical compositions thereof for the treatment of various conditions relating to production of collagen.

At present more than nineteen types of collagens have been identified. These collagens, including fibrillar collagen types I, II, III are synthesized as procollagen precursor molecules which contain amino- and carboxy-terminal peptide extensions. These peptide extensions, referred to as "pro-regions," are designated as N- and C- propeptides, respectively.

The pro-regions are typically cleaved upon secretion of the procollagen triple helical precursor molecule from the cell to yield a mature triple helical collagen molecule. Upon cleavage, the "mature" collagen molecule is capable of association, for example, into highly structured

collagen fibers. See e.g., Fessler and Fessler, 1978, *Annu. Rev. Biochem.* 47:129-162; Bornstein and Traub, 1979, in: *The Proteins* (eds. Neurath, H. and Hill, R.H.), Academic Press, New York, pp. 412-632; Kivirikko et al., 1984, in: *Extracellular Matrix Biochemistry* (eds. Piez, K.A. and Reddi, A.H.), Elsevier Science Publishing Co., Inc., New York, pp. 83-118; Prockop and Kivirikko, 1984, *N. Engl. J. Med.* 311:376-383; Kuhn, 1987, in: *Structure and Function of Collagen Types* (eds. Mayne, R. and Burgeson, R.E.), Academic Press, Inc., Orlando, Florida, pp. 1-42.

An array of conditions has been associated with the inappropriate or unregulated production of collagen, including pathological fibrosis or scarring, including endocardial sclerosis, idiopathic interstitial fibrosis, interstitial pulmonary fibrosis, perimuscular fibrosis, Symmers' fibrosis, pericentral fibrosis, hepatitis, dermatofibroma, cirrhosis such as biliary cirrhosis and alcoholic cirrhosis, acute pulmonary fibrosis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, kidney fibrosis/glomerulonephritis, kidney fibrosis/diabetic nephropathy, scleroderma/systemic, scleroderma/local, keloids, hypertrophic scars, severe joint adhesions/arthritis, myelofibrosis, corneal scarring, cystic fibrosis, muscular dystrophy (duchenne's), cardiac fibrosis, muscular fibrosis/retinal separation, esophageal stricture and Pyronie's disease. Further fibrotic disorders may be induced or initiated by surgery, including scar revision/plastic surgeries, glaucoma, cataract fibrosis, corneal scarring, joint adhesions, graft vs. host disease, tendon surgery, nerve entrapment, Dupuytren's contracture, OB/GYN adhesions/fibrosis, pelvic adhesions, peridural fibrosis, restenosis. Other conditions where collagen plays a key role include burns. Fibrosis of lung tissue is also observed in patients suffering from chronic obstructive airways disease (COAD) and asthma. One strategy for the treatment of these diseases and conditions is to inhibit the overproduction and/or deposition and/or unregulation of collagen. Thus, identification and isolation of molecules which control, inhibit and/or modulate the production and deposition of collagen are of major medical interest.

Recent evidence suggests that PCP is the essential key enzyme that catalyzes the cleavage of the Procollagen C-propeptide. This has been demonstrated in fibrillar collagens, including type I, type II, and type III collagen.

PCP was first observed in the culture media of human and mouse fibroblasts (Goldberg et al., 1975, *Cell* 4:45-50; Kessler and Goldberg, 1978, *Anal. Biochem.* 88:463-469), and chick tendon fibroblasts (Duskin et al., 1978, *Arch. Biochem. Biophys.* 185:326-332; Leung et al., 1979, *J. Biol. Chem.* 254:224-232). An acidic proteinase which removes the C-terminal propeptides from type I procollagen has also been identified (Davidson et al., 1979, *Eur. J. Biochem.* 100:551).

A partially purified protein having PCP activity was obtained from chick calvaria in 1982. Njieha et al., 1982, *Biochemistry* 23:757-764. In 1985, chicken PCP was isolated, purified and characterized from conditioned media of chick embryo tendons. Hojima et al., 1985, *J. Biol. Chem.* 260:15996-16003. Murine PCP has been subsequently purified from media of cultured mouse fibroblasts. Kessler et al., 1986, *Collagen Relat. Res.* 6:249-266; Kessler and Adar, 1989, *Eur. J. Biochem.* 186:115-121. Finally, the cDNA encoding human PCP has been identified, as set forth in the above-referenced articles and references disclosed therein.

Experiments conducted with these purified forms of chick and mouse PCP have indicated that the enzyme is instrumental in the formation of functional collagen fibers. Fertala et al., 1994, *J. Biol. Chem.* 269:11584.

As a consequence of the enzyme's apparent importance to collagen production, scientists have identified a number of PCP inhibitors. See e.g., Hojima et al., supra. For example, several metal chelators have demonstrated activity as PCP inhibitors. Likewise, chymostatin and pepstatin A were found to be relatively strong inhibitors of PCP. Additionally,  $\alpha_2$ -Macroglobuline, ovostatin, and fetal bovine serum appear to at least partially inhibit PCP activity.

Dithiothreitol, SDS, concanavalin A,  $Zn^{2+}$ ,  $Cu^{2+}$ , and  $Cd^{2+}$  are similarly reported to be inhibitory at low concentrations. Likewise, some reducing agents, several amino acids, phosphate, and ammonium sulfate were inhibitory at concentrations of 1-10mM. Further, the enzyme was shown to be inhibited by the basic amino acids lysine and arginine (Leung et al., supra; Ryh nen et al., 1982, *Arch. Biochem. Biophys.* 215:230-235). Finally, high concentrations of NaCl or Tris-HCl buffer were found to inhibit PCP's activity. For example, it is reported that, with 0.2, 0.3, and 0.5M NaCl, the activity of PCP was reduced 66, 38, and 25%, respectively, of that observed with the standard assay concentration of 0.15M. Tris-HCl buffer in a concentration of 0.2-0.5M markedly inhibited activity (Hojima et al., supra). PCP activity and its inhibition have been determined using a wide array of assays. See e.g., Kessler and Goldberg, 1978, *Anal. Biochem.* 86:463; Njieha et al., 1982, *Biochemistry* 21:757-764. As articulated in numerous publications, the enzyme is difficult to isolate by conventional biochemical means and the identity of the cDNA sequence encoding such enzyme was not known until reported in the above referenced and related patent applications.

In view of its essential role in the formation and maturation of collagen PCP appears to be an ideal target for the treatment of disorders associated with the inappropriate or unregulated production and maturation of collagen.

The identification of effective compounds which specifically inhibit the activity of PCP to regulate and modulate abnormal or inappropriate collagen production is therefore desirable and the object of this invention.

- 5 Matrix metalloproteinases (MMPs) constitute a family of structurally similar zinc-containing metalloproteinases, which are involved in the remodelling, repair and degradation of extracellular matrix proteins, both as part of normal physiological processes and in pathological conditions.

- Another important function of certain MMPs is to activate other enzymes, including other MMPs, by cleaving the pro-domain from their protease domain. Thus, certain MMPs act to regulate the activities of other MMPs, so that over-production in one MMP may lead to excessive proteolysis of extracellular matrix by another, e.g. MMP-14 activates pro-MMP-2
- 10

- During the healing of normal and chronic wounds, MMP-1 is expressed by migrating keratinocytes at the wound edges (U.K. Saarialho-Kere, S.O. Kovacs, A.P. Pentland, J. Clin. Invest. 1993, 92, 2858-66). There is evidence which suggests MMP-1 is required for keratinocyte migration on a collagen type I matrix in vitro, and is completely inhibited by the presence of the non-selective MMP inhibitor SC44463 ((N4-hydroxy)-N1-[(1S)-2-(4-methoxyphenyl)methyl-1-((1R)-methylamino)carbonyl)]-(2R)-2-(2-methylpropyl)butanediamide) (B.K. Pilcher, J.A. Dumin, B.D. Sudbeck, S.M. Krane, H.G. Welgus, W.C. Parks, J. Cell Biol., 1997, 137, 1-13). Keratinocyte migration in vivo is essential for effective wound healing to occur.
- 20

- MMP-2 and MMP-9 appear to play important roles in wound healing during the extended remodelling phase and the onset of re-epithelialisation, respectively ( M.S. Agren, Brit. J. Dermatology, 1994, 131, 634-40; T. Salo, M. Mäkinen, M. Kylmäniemi, Lab. Invest., 1994, 70, 176-82). The potent, non-selective MMP inhibitor BB94 ((2S,3R)-5-methyl-3-(((1S)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-[(2-thienylthio)methyl]hexanohydroxamic acid, batimastat), inhibits endothelial cell invasion of basement membrane, thereby inhibiting angiogenesis (G. Tarboletti, A. Garofalo, D. Belotti, T. Drudis, P. Borsotti, E. Scanziani, P.D. Brown, R. Giavazzi, J. Natl. Cancer Inst., 1995, 87, 293-8). There is evidence that this process requires active MMP-2 and/or 9.
- 25
- 30

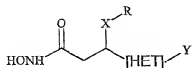
- Thus PCP inhibitors which significantly inhibit MMPs 1 and/or 2 and/or 9 would be expected to impair wound healing. MMP-14 is responsible for the activation of MMP-2, and thus inhibition of MMP-14 might also result in impaired wound healing.
- 35

For recent reviews of MMPs, see Zask et al, *Current Pharmaceutical Design*, 1996, 2, 624-661; Beckett, *Exp. Opin. Ther. Patents*, 1996, 6, 1305-1315; and Beckett et al, *Drug Discovery Today*, vol 1(no.1), 1996, 16-26.

- 5 Alternative names for various MMPs and substrates acted on by these are shown in the table below (Zask et al, *supra*).

Enzyme	Other names	Preferred substrates
MMP-1	Collagenase-1, interstitial collagenase	Collagens I, II, III, VII, X, gelatins
MMP-2	Gelatinase A, 72kDa gelatinase	Gelatins, collagens IV, V, VII, X, elastin, fibronectin; activates pro-MMP-13
MMP-3	Stromelysin-1	Proteoglycans, laminin, fibronectin, gelatins.
MMP-7	Pump, Matrilysin	Proteoglycans, laminin, fibronectin, gelatins, collagen IV, elastin, activates pro-MMP-1 and -2.
MMP-8	Collagenase-2, neutrophil collagenase	Collagens I, II, III
MMP-9	Gelatinase B, 92 kDa gelatinase	Gelatins, collagens IV, V, elastin
MMP-12	Macrophage metalloelastase	Elastin, collagen IV, fibronectin, activates pro-MMP-2 & 3.
MMP-13	Collagenase-3	Collagens I, II, III, gelatins
MMP-14	MT-MMP-1	Activates pro-MMP-2 & 13, gelatins
MMP-15	MT-MMP-2	unknown
MMP-16	MT-MMP-3	Activates pro-MMP-2
MMP-17	MT-MMP-4	unknown

- International Patent Applications PCT/IB00/01855 (published as WO 01/47901) and PCT/IB01/02360 (filed on 7<sup>th</sup> December 2001), and foreign equivalents thereof, describe various 3-heterocycylpropanohydroxamic acid PCP inhibitors. The teachings of these documents are herein incorporated by reference in their entirety.
- 15 According to one aspect of the present invention, there are provided compounds of formula (I):



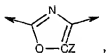
(I)

wherein:

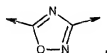
X is C<sub>1-6</sub> alkylene or C<sub>2-6</sub> alkenylene, each of which is optionally substituted by one or more fluorine atoms;

R is aryl, C<sub>5-8</sub> cycloalkenyl or C<sub>3-8</sub> cycloalkyl optionally substituted by one or more fluorine atoms;

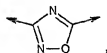
[HET] is a divalent heterocyclic moiety selected from



or



or



Z is H or C<sub>1-4</sub> alkyl,

Y is a mono- or bicyclic unsaturated ring system containing from 5 to 10 ring atoms, of which up to 4 which are hetero-atoms independently selected from N, O and S, and which ring system is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> or het<sup>1</sup>,

R<sup>1</sup> and R<sup>2</sup> are each independently selected from H and C<sub>1-4</sub> alkyl optionally substituted by C<sub>1-4</sub> alkoxy,

het<sup>1</sup> is a N-linked 4- to 6-membered mono- or bicyclic heterocycle optionally containing 1 or 2 further hetero ring atoms independently selected from N and O, which heterocycle is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> or het<sup>2</sup>,

het<sup>2</sup> is a N-linked 4- to 6-membered mono- or bicyclic heterocycle optionally containing 1 or 2 further hetero ring atoms independently selected from N and O,

"aryl" is phenyl optionally substituted by one or more substituents independently selected from R<sup>3</sup>, OH, SO<sub>2</sub>(C<sub>1-4</sub> alkyl) and/or C(O)<sub>2</sub>(C<sub>1-4</sub> alkyl) groups,

and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

"Alkyl", "alkylene", "alkoxy", "alkanoyl", and "alkenylene" groups, including in groups

- 5 incorporating said moieties, may be straight chain or branched where the number of carbon atoms allows.

Halogen is taken to mean fluorine, chlorine, bromine or iodine.

- 10 Pharmaceutically-acceptable salts are well known to those skilled in the art, and for example include those mentioned in the art cited above, and by Berge et al, in J.Pharm.Sci., 66, 1-19 (1977). Suitable acid addition salts are formed from acids which form non-toxic salts and include the hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate, bisulphate, phosphate, hydrogenphosphate, acetate, trifluoroacetate, gluconate, lactate, salicylate, citrate, tartrate,
- 15 ascorbate, succinate, maleate, fumarate, gluconate, formate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, pamoate, camsylate, and p-toluenesulphonate salts.

Pharmaceutically acceptable base addition salts are well known to those skilled in the art, and for example include those mentioned in the art cited above, and can be formed from bases

20 which form non-toxic salts and include the aluminium, calcium, lithium, magnesium, potassium, sodium and zinc salts, and salts of non-toxic amines such as diethanolamine.

Certain of the compounds of formula (I) may exist in one or more zwitterionic forms. Certain of the compounds of formula (I) may exist in one or more tautomeric forms. Certain of the

25 compounds of formula (I), their salts, solvates, prodrugs, etc. may exist in one or more polymorphic forms. It is to be understood that the compounds of formula (I) include all such zwitterions, tautomers and polymorphs..

The compounds of formula (I), their salts, hydrates, prodrugs etc. can exhibit isotopic variation,

30 e.g. forms with enriched  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ , etc. may be prepared, for example by suitable variation of the synthetic methods described herein using methods and reagents known in the art or routine modification thereof. All such isotopic variants are included in the scope of the invention.

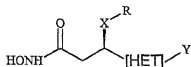
- 35 Prodrug moieties are well-known to those skilled in the art (see for example the article by H Feres, in *Drugs of Today*, vol 19, no.9 (1983) pp.499-538, especially section A1), and for example include those specifically mentioned in A.A. Sinkula's article in *Annual Reports in*



Medicinal Chemistry, vol 10, chapter 31, pp.306-326, herein incorporated by reference, and the references therein. Specific prodrug moieties which may be specifically mentioned are aliphatic-aromatic, carbonate, phosphate and carboxylic esters, carbamates, peptides, glycoside, acetals and ketals, tetrahydropyranyl and silyl ethers. Such prodrug moieties can be cleaved in situ, e.g. are hydrolysable in physiological conditions, to give compounds of formula (I).

Certain of the compounds of the formula (I) may exist as geometric isomers. The compounds of the formula (I) may possess one or more asymmetric centres, apart from the specified centres in formula (I), and so exist in two or more stereoisomeric forms. The present invention includes all the individual stereoisomers and geometric isomers of the compounds of formula (I) and mixtures thereof.

Preferably the compounds of formula (I) have the following stereochemistry (IA):



(IA)

Preferably X is a linear  $C_{2-6}$  alkylene moiety optionally substituted by one or more fluorine atoms. More preferably X is propylene.

Preferably [HET] is



Preferably R is  $C_{3-6}$  cycloalkyl optionally substituted by one or more fluorine atoms.

More preferably R is cyclobutyl, cyclopentyl or cyclohexyl optionally substituted by one or more fluorine atoms.

Most preferably R is cyclohexyl.

Preferably Y is a 5- or 6-membered unsaturated ring containing 0, 1 or 2 ring hetero-atoms independently selected from N and O,

and which ring is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> and het<sup>1</sup>.

- 5 More preferably Y is a 5- or 6-membered unsaturated ring containing 0, 1 or 2 ring hetero-atoms independently selected from N and O,  
and which ring is optionally substituted by one or more substituents independently selected from =O, CONH<sub>2</sub>, CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, CH<sub>3</sub>, NH<sub>2</sub>, CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, CO<sub>2</sub>H, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, NHCH<sub>3</sub>, NHC<sub>2</sub>H<sub>5</sub>, N(CH<sub>3</sub>)<sub>2</sub>, morpholino, imidazol-1-yl, methoxy, ethoxy and NHSO<sub>2</sub>CH<sub>3</sub>.
- 10 Yet more preferably Y is 5-carbamoylpyridin-3-yl, uracil-5-yl, pyridin-4-yl, 6-methylpyridin-3-yl, 5-carboxypyridin-3-yl, 6-methoxycarbonylmethylpyridin-3-yl, 6-(4-methylpiperazino)pyridin-3-yl, 6-(3-dimethylaminoazetidino)pyridin-3-yl, 6-(3-morpholinoazetidino)pyridin-3-yl, 4-carboxypyridin-2-yl, 6-dimethylaminopyridin-3-yl, 6-(imidazol-1-yl)pyrazin-2-yl, 3-morpholinopyrazin-2-yl, 3-pyrrolidinopyrazin-2-yl, 3-dimethylaminopyrazin-2-yl, 3-methylaminopyrazin-2-yl, 3-
- 15 methylsulphonamidophenyl, 3-carboxyphenyl or 6-ethoxypyrazin-2-yl.

Most preferably Y is uracil-5-yl or 4-carboxypyridin-2-yl.

- A preferred group of compound of formula (I) are those wherein each substituent is as specified  
20 in the Examples below.

Another preferred group are the compounds of the Examples below and the salts, solvates and prodrugs thereof. Especially preferred are the compounds of Examples 1 and 25 and the salts, solvates and prodrugs thereof.

- 25 A further aspect of the invention is a PCP inhibitor of formula (I) which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14.
- A further aspect of the invention is the use of a PCP inhibitor of formula (I) which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14 in medicine.
- 30 Further related to this aspect of the invention is the use of a PCP inhibitor of formula (I) which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14 in the manufacture of an antiscarring medicament.
- Further related to this aspect of the invention is a method of treating a condition mediated by PCP and in which MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14 have a beneficial effect,  
35 with an effective amount of PCP inhibitor of formula (I) which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14, an example of such a condition being a wound.

Preferably the PCP inhibitor of formula (I) mentioned in this aspect of the invention is selective against at least MMP-1, MMP-2 and MMP-9.

Most preferably the said PCP inhibitor of formula (I) is selective against MMP-1, MMP-2, MMP-9, and MMP-14.

- 5 Preferably the said selective PCP inhibitor of formula (I) has an  $IC_{50}$  vs. PCP of 0.5 $\mu$ M or lower, and selectivities vs. MMP-2 and MMP-9 of at least 30-fold, in the tests described herein.

Preferably the selective PCP inhibitor of formula (I) has an  $IC_{50}$  vs. PCP of 0.1 $\mu$ M or lower, and selectivities vs. MMP-1, MMP-2, MMP-9 and MMP-14 of at least 300-fold, in the tests described herein.

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Another aspect of the invention is a substance of formula (I) described herein, including the salts, solvates and prodrugs thereof, for use in medicine.

15

Another aspect of the invention is a substance of formula (I) described herein, including the salts, solvates and prodrugs thereof, for use in treating a PCP-mediated condition, such as in an antiscarring medicament.

20

Another aspect of the invention is the use of the substances of formula (I) described herein, including the salts, solvates and prodrugs thereof, in the manufacture of a medicament for treatment of a PCP-mediated condition (e.g. an antiscarring medicament).

25

Another aspect of the invention is a pharmaceutical composition comprising a compound of formula (I), salts thereof, solvates thereof and/or prodrugs thereof, and a pharmaceutically acceptable diluent, carrier or adjuvant.

30

Another aspect of the invention is the combination of a compound of formula (I), or a salt, solvate or prodrug thereof, with another material useful in treating wounds, such as:  
(i) a growth factor such as TGF- $\beta$ -3 (Renovo), IGF-1 (Genentech), IGF-1 complex (Celtrix), KGF-2 or FGF-10 (Sumitomo), DWP-401/EGF (Daewoong) or SNK-863 (Sanwa Kagaku Kenkyusho);

35

(ii) a growth factor agonist such as Noggin (Regeneron);  
(iii) a growth factor antibody/antisense material, such as those to: TGF- $\beta$ -1 or 2 (Renovo, CaT), PDGF (II Yang) or CTGF (Fibrogen);  
(iv) a hormone such as DHEAS (Pharmadigm), ConXn / Relixin (Connetics);  
(v) an antibody to adhesion compounds such as ICAM-1 (Boehringer);  
(vi) a MMP beneficial to healing of wounds, such as Collagenase ABC (BioSpecifics);  
(vii) a barrier such as ADCON (Gliatech);

- (viii) skin products such as artificial skin systems such as those based on DermaGraft (Advanced Tissue Sciences Inc.), INTEGRA Artificial Skin (Integra Life Sciences Holding Corp.), cell cultures such as Apligraf / Graftskin (Novartis), those developed by Cell Genesys Inc., AlloDerm (LifeCell) or matrix formulation products such as Argidene gel (Telios Pharmaceuticals Inc.);
- (ix) a uPA inhibitor such as those disclosed in WO 99/01451;
- (x) a MMP-3 inhibitor such as those disclosed in WO99/35124, WO 99/29667 and WO 00/74681;

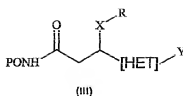
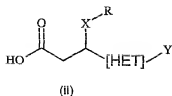
Yet another aspect of the invention is a method of treatment of a condition mediated by PCP comprising administration of a therapeutically-effective amount of a substance according to the above definitions.

It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of PCP-mediated conditions and diseases.

The invention further provides Methods for the production of compounds of the invention, which are described below and in the Examples and Preparations. The skilled man will appreciate that the compounds of the invention could be made by methods other than those specifically described herein, by adaptation of the methods herein described in the sections below and/or adaptation thereof, for example by methods known in the art. Suitable guides to synthesis, functional group transformations, use of protecting groups, etc. are, for example, "Comprehensive Organic Transformations" by RC Larock, VCH Publishers Inc. (1989), "Advanced Organic Chemistry" by J March, Wiley Interscience (1985), "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978), "Organic Synthesis - The Disconnection Approach" by S Warren, Wiley Interscience (1982), "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982), "Protective Groups In Organic Synthesis" by TW Greene and PGM Wuts, John Wiley and Sons Inc. (1999), and P.J. Koelsch, In "Protecting Groups", Georg Thieme Verlag (1994), and any updated versions of said standard works.

In the Methods below, unless otherwise specified, the substituents are as defined above with reference to the compounds of formula (I) above.

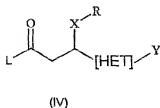
The compounds of formula (I) may be made from the corresponding acids of formula (II) or the corresponding protected N-hydroxy acid species (III), where "P" is a suitable NHO-protecting group such as those mentioned in Greene and Wuts, *supra*. Of particular interest are compounds of formula (III) where "P" is a tri(C<sub>1-4</sub> alkyl)silyl group such as trimethylsilyl (TMS).



Deprotection of compounds of formula (III) to give compounds of formula (I) can be carried out using a suitable deprotection regime. For example, when P is TMS, an acidic hydrolysis can be used, such as reaction with methanolic hydrochloric acid or aqueous citric acid.

Transformation of acids (II) into compounds of formula (I) can be carried out using a number of methods, such as reaction with carbonyldiimidazole and a suitable base such as triethylamine, in a suitable solvent such as tetrahydrofuran (THF), followed by reaction with hydroxylamine ( $\text{NH}_2\text{OH}$ , suitably generated from a salt thereof, such as the hydrochloride, in the presence of a suitable base such as a tertiary amine, for example triethylamine).

Alternatively, acids (II) can be transformed into activated acid derivatives (IV), where L is a suitable leaving group such as  $\text{OCO}(\text{C}_{1-4} \text{ alkyl})$  or imidazolyl, which can then be reacted with a protected hydroxylamine species " $\text{PONH}_2$ ", to give compounds of formula (III), above. Suitable examples of this transformation include reaction of the acid (II) with a suitable chloro-ester such as isobutyl chloroformate, with a suitable base, e.g. a tertiary amine such as triethylamine or N-methylmorpholine to give an activated acid (IV), where L is  $\text{OCO}(\text{isobutyl})$ . Suitable examples of preparation of compounds of formula (IV) where L is imidazolyl include reaction of acid (II) with carbonyldiimidazole in a suitable solvent such as methylene chloride, or with carbonyldiimidazole with a suitable tertiary amine base such as triethylamine in a suitable ether solvent such as THF.

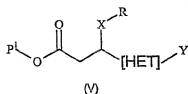


The compounds of formula (IV) can be transformed into compounds of formula (III) by reaction with compounds of formula  $\text{PONH}_2$ , where P is as described earlier.

Compounds of formula (I) may also be made directly from compounds of formula (IV) by reaction with hydroxylamine, suitably generated in situ from a salt thereof (e.g. hydrochloride salt) and a suitable base such as a tertiary amine (e.g. triethylamine).

- 5 Compounds of formula (III) can be transformed into compounds of formula (I) as described earlier.

Compounds of formula (II) can be made by deprotection of the compounds of formula (V) where P<sup>1</sup> is a suitable carboxylic acid protecting group such as t-butyl, with a suitable deprotecting regime. For example when P<sup>1</sup> is t-butyl, the deprotection can be carried by reaction with trifluoroacetic acid.

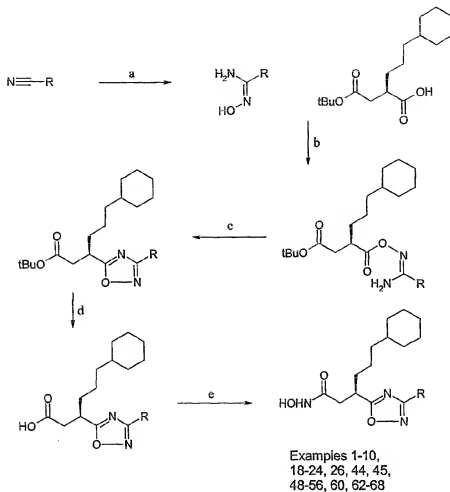


10

Certain compounds of formula (I) may be transformed into other compounds of formula (I) by suitable functional group interconversion (FGI) of a type well-known to those skilled in the art. For examples where the compound of formula (I) contains an ester or acid moiety, these can be interconverted readily by known hydrolysis or esterification methods respectively. Hydrolysis of an ethyl ester is exemplified in Example 11 below which mentions the use of lithium hydroxide as base. Another example of an interconversion of compounds of formula (I) is where one compound of formula (I) contains what could be regarded as a protecting group and the interconversion can be regarded as a deprotection - e.g. Example 33 below describes the conversion of a t-butoxycarbonylamino compound (of Example 32) into the corresponding free amine using trifluoroacetic acid (TFA). Many other FGIs of compounds of formula (I) into other compounds of formula (I) are possible using methods exemplified in the Examples and Preparations sections below, and standard FGI chemistry known in the art.

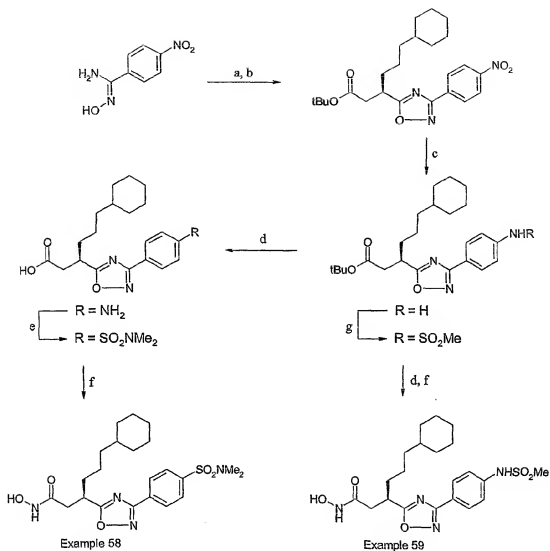
- 15  
20  
25 The compounds of formula (I), (II), (III) and (IV) may be made by methods outlined in Schemes 1-11 below, or by analogous methods.

Scheme 1



- 5    <sup>a</sup>(a),  $\text{HONH}_2$ ; (b), CDI or WSCDI/HOBT or WSCDI/4-DMAP; (c), Xylene 130 °C or neat 130 °C; (d), TFA; (e),  $\text{iBuOCOCl}$  or CDI, then  $\text{TMSONH}_2$ , then MeOH or 2M HCl, or  $\text{HONH}_2$ .

Scheme 2.



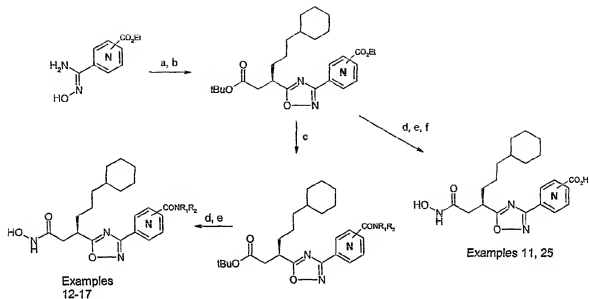
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(a), CDI or WSCDI/HOBT or WSCDI/4-DMAP; (b), Xylene 130 °C or neat 130 °C; (c), SnCl<sub>2</sub>; (d), TFA; (e), i, CHCl<sub>3</sub>, NaNO<sub>2</sub>, ii, SO<sub>2</sub>, CuCl<sub>2</sub>, iii, NHMe<sub>2</sub>; (f), iBuOCOCi or CDI, then TMSONH<sub>2</sub>, then MeOH, or HONH<sub>2</sub>; (g), MeSO<sub>2</sub>Cl.

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Scheme 3.

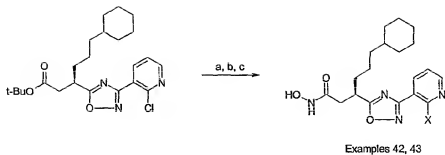


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(a),  $\text{CDI}$  or  $\text{WSCDI/HOBT}$  or  $\text{WSCDI/4-DMAP}$ ; (b),  $\text{Xylene}$   $130^\circ\text{C}$  or neat  $130^\circ\text{C}$ ; (c),  $\text{NHR}_1\text{R}_2$ ; (d)  $\text{TFA}$ ; (e),  $\text{iBuOCOC}$  or  $\text{CDI}$ , then  $\text{TMSONH}_2$ , then  $\text{MeOH}$ , or  $\text{HONH}_2$ ; (f)  $\text{LiOH}$ .

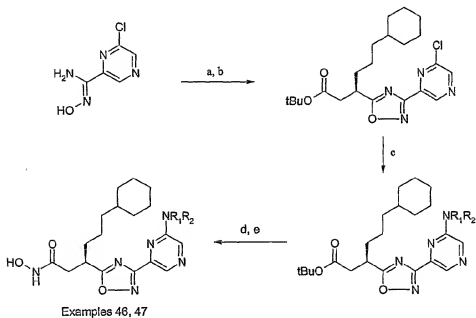


Scheme 5.



- 5 (a), TFA; (b),  $\text{NHR}_1\text{R}_2$ , (c)  $\text{iBuOCOC}$  or  $\text{CDI}$ , then  $\text{TMSONH}_2$ , then  $\text{MeOH}$ , or  $\text{HONH}_2$ .

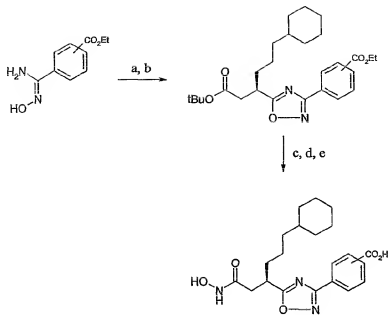
Scheme 6.



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- (a),  $\text{CDI}$  or  $\text{WSCDI/HOBT}$  or  $\text{WSCDI/4-DMAP}$ ; (b), Xylene  $130^\circ\text{C}$  or neat  $130^\circ\text{C}$ ; (c), TFA; (d),  $\text{NHR}_1\text{R}_2$ ; (e),  $\text{iBuOCOC}$  or  $\text{CDI}$ , then  $\text{TMSONH}_2$ , then  $\text{MeOH}$ , or  $\text{HONH}_2$ .

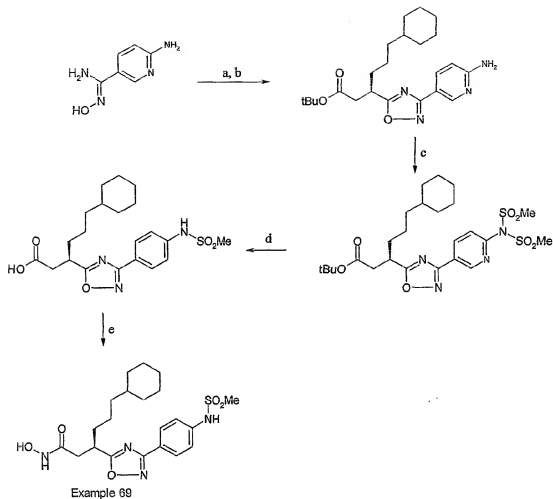
Scheme 7.



Examples 57, 61

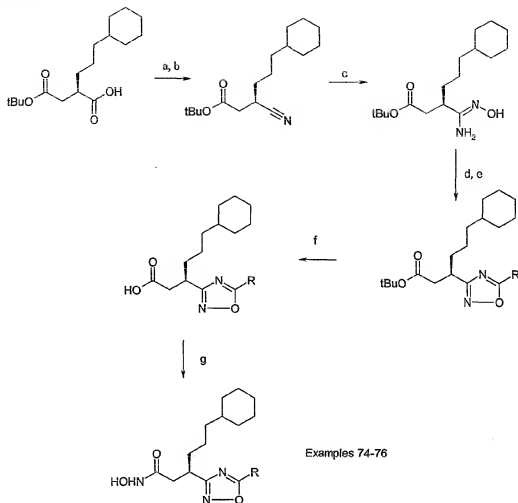
- 5 (a), CDI or WSCDI/HOBT or WSCDI/4-DMAP; (b), Xylene 130 °C or neat 130 °C; (c), TFA; (d),  $\text{iBuOCOCl}$  or CDI, then  $\text{TMSONH}_2$ , then MeOH, or  $\text{HONH}_2$ ; (e) LiOH.

Scheme 8.



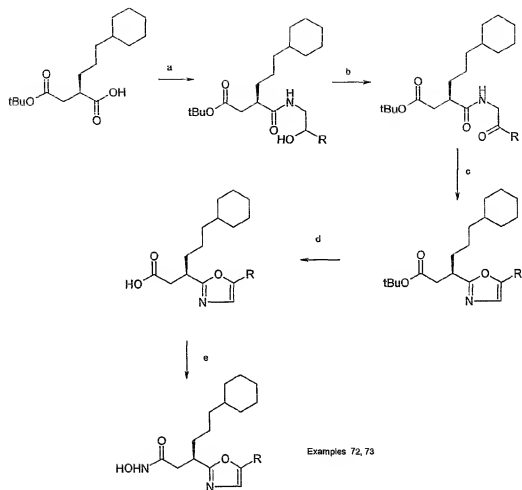
(a), CDI or WSCDI/HOBT or WSCDI/4-DMAP; (b), Xylene 130 °C or neat 130 °C; (c), MeSO<sub>2</sub>Cl; (d), NaOH; (e), iBuOCOCi or CDI, then TMSONH<sub>2</sub>, then MeOH, or HONH<sub>2</sub>.

Scheme 9



- 5      <sup>a</sup>(a),  $i\text{BuOCOC}l$  then ammonia (b), TFAA, pyridine; (c),  $\text{HONH}_2 \cdot \text{HCl}$ , N-methylmorpholine, ethanol, reflux; (d), WSCDI, DMAP,  $\text{RCO}_2\text{H}$ ; (e),  $140^\circ\text{C}$ , (f) TFA, (g)  $i\text{BuOCOC}l$ , N-methylmorpholine,  $\text{HONH}_2 \cdot \text{HCl}$  or  $\text{HOBT}$ , WSCDI, aqueous  $\text{HONH}_2$ .

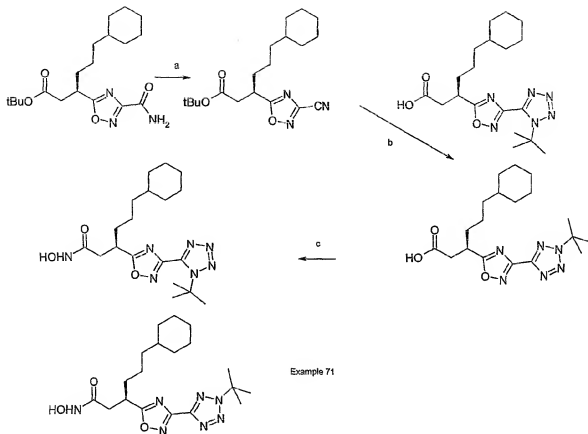
Scheme 10



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(a),  $\text{WSCDI/HOBT} + \text{RCH(OH)CH}_2\text{NH}_2$ ; (b), Dess-Martin periodinane; (c), triflic anhydride, triphenylphosphine oxide, triethylamine; (d), TFA; (e),  $i\text{BuOCOCi}$  or  $\text{CDI}$ , then  $\text{TMSNH}_2$ .

Scheme 11



5

(a), TFAA, pyridine; (b), TMS-azide; (c), HOAt, WSCDI, TMSONH<sub>2</sub>.

10 It will be apparent to those skilled in the art that other protection and subsequent deprotection regimes during synthesis of a compound of the invention may be achieved by conventional techniques, for example as described in the volumes by Greene and Wuts, and Kocienski, *supra*, some of which are mentioned specifically herein.

15 Where desired or necessary the compound of formula (I) is converted into a pharmaceutically acceptable salt thereof. A pharmaceutically acceptable salt of a compound of formula (I) may be conveniently be prepared by mixing together solutions of a compound of formula (I) and the desired acid or base, as appropriate. The salt may be precipitated from solution and collected by filtration, or may be collected by other means such as by evaporation of the solvent.

20



Compounds of the invention are available by either the methods described herein in the methods, schemes, Examples and Preparations or suitable adaptation thereof using methods known in the art. It is to be understood that the synthetic transformation methods mentioned herein may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound.

The compounds, salts, solvates (including hydrates) and prodrugs of the invention may be separated and purified by conventional methods.

Separation of diastereomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereomeric salts formed by reaction of the corresponding racemate with a suitably optically active acid or base. In certain cases preferential crystallisation of one of the enantiomers can occur from a solution of a mixture of enantiomers, thus enriching the remaining solution in the other enantiomer.

For human use, the compounds of formula (I) or their salts can be administered alone, but will generally be administered in admixture with a pharmaceutically acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. The compound or salt could be incorporated into capsules or tablets for targeting the colon or duodenum via delayed dissolution of said capsules or tablets for a particular time following oral administration. Dissolution could be controlled by susceptibility of the formulation to bacteria found in the duodenum or colon, so that no substantial dissolution takes place before reaching the target area of the gastrointestinal tract. The compounds or salts can be injected parenterally, for example, intravenously, intramuscularly, intradermally or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution or suspension which may contain other substances, for example, enough salt or glucose to make the solution isotonic with blood. They can be administered topically, or transdermally, in the form of creams, gels, suspensions, lotions, ointments, dusting powders, sprays, foams, mousses, drug-incorporated dressings, solutions, sponges, fibres,

microemulsions, films, skin patches, ointments such as petrolatum or white soft paraffin based ointments or via a skin patch or other device. Penetration enhancers may be used, and the compound may be used in combination with cyclodextrins. In addition, the compound may be delivered using iontophoresis, electroporation, phonophoresis or sonophoresis. They could be administered directly onto a wound site. They could be incorporated into a coated suture. For example they can be incorporated into a lotion or cream consisting of an aqueous or oily emulsion of mineral oils; sorbitan monostearate; polysorbate 60; cetyl esters wax; cetearyl alcohol; 2-octyldodecanol; benzyl alcohol; water; polyethylene glycols and/or liquid paraffin, or they can be incorporated into a suitable ointment consisting of one or more of the following - mineral oil; liquid petrolatum; white petrolatum; propylene glycol; polyoxyethylene polyoxypropylene compound; emulsifying wax and water, or as hydrogel with cellulose or polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA, CFC, CO<sub>2</sub> or other suitable propellant, optionally also including a lubricant such as sorbitan trioleate, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycols impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings. The compound or salt could also be administered intraocularly for ophthalmic use e.g. via intraocular injection, or sustained release device or in a lens implant, via subconjunctival injection, or as an eye drop with appropriate buffers, viscosity modifiers (e.g. cellulose or polyacrylate derivatives), preservatives (e.g. benzalkonium chloride (BZK)) and agents to adjust tonicity (e.g. sodium chloride). Such formulation techniques are well-known in the art.

For certain uses, vaginal, rectal and nasal (e.g. by inhalation of a dry powder or aerosol) administration would be suitable.

All such formulations may also contain appropriate stabilisers and preservatives.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of formula (I) or their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.1 to 10, and most preferably from 0.5 to 5 mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time as appropriate.

#### Ocular Formulation

The compounds or their salts, solvates or prodrugs may be administered topically by the ocular route. They may be formulated as sterile, isotonic, pH adjusted, buffered suspensions or solutions. A polymer may be added such as cross-linked polyacrylic acid, polyvinylalcohol,

hyaluronic acid, a cellulosic polymer (e.g. hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), or a heteropolysaccharide polymer (e.g. gelatin gum). Alternatively, they may be formulated in an ointment such as petrolatum or mineral oil, incorporated into bio-degradable (e.g. absorbable gel sponges, collagen) or non-biodegradable (e.g. silicone) implants, lenses or delivered via particulate or vesicular systems such as niosomes or liposomes. Formulations may be optionally combined with a preservative, such as benzalkonium chloride. In addition, they may be delivered using iontophoresis. The compound may also be used in combination with cyclodextrins.

- 10 An example of preferred formulation excipients of a compound, salt, solvate or prodrug according to the invention:

Ingredients	% (w/w) composition
$\text{NaH}_2\text{PO}_4$	0.370
15 $\text{Na}_2\text{HPO}_4$	0.567
Glycine	0.430
Carbomer 940	1.000
Water	to 100
pH adjusted to ~7	

20

The preferred formulation will be a buffered solution (preferably using monobasic and dibasic sodium phosphate) containing 0.5 to 5.0% of a cross-linked polyacrylic acid, pH adjusted to around 7 with the addition of a stabiliser such as glycine.

- 25 For topical administration to human patients with acute/surgical wounds or scars, the daily dosage level of the compounds, in suspension or other formulation, could be from 0.01 to 50mg/ml, preferably from 0.3 to 30 mg/ml.

- 30 The dosage will vary with the size of the wound, whether or not the wound is open or closed or partially closed, and whether or not the skin is intact.

- 35 The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient, as well as the efficacy of the drug compound. The above dosages are exemplary of the average case; there can of course be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

### Biological Test Methods

#### PCP Inhibition

- 5 In order to determine potency of PCP inhibitors a fluorogenic PCP cleavage assay was used. This assay is based on the template of Beekman et al. (FEBS Letters (1996), 390: 221-225) using a fluorogenic substrate. The substrate (Dabcyi-Arg-Tyr-Tyr-Arg-Ala-Asp-Asp-Ala-Asn-Val-Glu(EDANS)-NH<sub>2</sub>) contains the cleavage site of human PCP (Hojima et al., J Biol Chem (1985), 260: 15996-16003). Human PCP has been purified from supernatant of stable transfected CHO
- 10 cells using hydrophobic interaction column followed by Superdex 200 gel filtration. 4 µg total protein of this enzyme preparation was incubated with various concentrations of the substance to be tested and 3x 10<sup>-6</sup> M substrate in assay buffer (50 mM Tris-Base, pH 7.6 containing 150 mM NaCl, 5 mM CaCl<sub>2</sub>, 1µM ZnCl<sub>2</sub> and 0.01 % Brij 35). The assay was performed in 96-well black fluorimeter plates and fluorescence was read continuously in a fluorimeter over 2.5 hours
- 15 (λ<sub>ex</sub> = 340 nm, λ<sub>em</sub> = 485 nm) at a constant 37°C with shaking. Release of the fluorogenic signal was in linear correlation to PCP activity. Reading of the mean velocity from 30 min after start of experiment until 2.5 hours was calculated by the Biolise software. IC<sub>50</sub> values were calculated by plotting % inhibition values against compound concentration using Tessella add in for Excel
- 20 spreadsheet. Example compounds were tested and were found to have IC<sub>50</sub> values vs. PCP of 1µM or less.

#### MMP Inhibition

- 25 The ability of compounds to inhibit the cleavage of fluorogenic peptides by MMPs 1, 2, 9, and 14 is described below.

The assays for MMPs 2, 9, and 14 are based upon the original protocol described by Knight et al. (Fed.Euro.Biochem.Soc., 296 (3), 283-286; 1992) with the slight modifications given below.

#### 30 Inhibition of MMP-1

##### (i) Enzyme Preparation

- Catalytic domain MMP-1 was prepared at Pfizer Central Research. A stock solution of MMP-1 (1µM) was activated by the addition of aminophenylmercuric acetate (APMA), at a final
- 35 concentration of 1mM, for 20 minutes at 37°C. MMP-1 was then diluted in Tris-HCl assay buffer (50mM Tris, 200mM NaCl, 5mM CaCl<sub>2</sub>, 20µM ZnSO<sub>4</sub>, 0.05% Brij 35) pH 7.5 to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

(ii) Substrate

The fluorogenic substrate used in this assay was Dnp-Pro- $\gamma$ -cyclohexyl-Ala-Gly-Cys(Me)-His-Ala-Lys(N-Me-Ala)-NH<sub>2</sub> as originally described by Bickell et al (Anal. Biochem, 212, 58-64, 1993).

5 The final substrate concentration used in the assay was 10 $\mu$ M.

(iii) Determination of Enzyme Inhibition

Test compounds were dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to  
10 each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence (substrate cleavage) using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 355nm and emission wavelength of 440nm. The potency of inhibitors was measured from the amount of substrate  
15 cleavage obtained using a range of test compound concentrations, and, from the resulting dose-response curve, an IC<sub>50</sub> value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-2 and MMP-9

20

(i) Enzyme Preparation

Catalytic domain MMP-2 and MMP-9 were prepared at Pfizer Central Research. A stock solution of MMP-2 / MMP-9 (1 M) was activated by the addition of aminophenylmercuric acetate (APMA). For MMP-2 and MMP-9, a final concentration of 1mM APMA was added, followed by  
25 incubation for 1 hour at 37°C. The enzymes were then diluted in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM CaCl<sub>2</sub> and 0.16% Brij 35, pH 7.5), to a concentration of 10nM. The final concentration of enzyme used in the assays was 1nM.

(ii) Substrate

The fluorogenic substrate used in this screen was Mca-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH<sub>2</sub> (Bachem Ltd, Essex, UK) as originally described by Nagase et al (J.Biol.Chem., 269(33), 20952-20957, 1994). This substrate was selected because it has a balanced hydrolysis rate against MMPs 2 and 9 ( $k_{cat} / k_m$  of 54,000, 59,400 and 55,300 s<sup>-1</sup> M<sup>-1</sup> respectively). The final  
30 substrate concentration used in the assay was 5 $\mu$ M.

35 (iii) Determination of Enzyme Inhibition

Test compounds were dissolved in dimethyl sulphoxide and diluted with test buffer solution (as above) so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 328nm and emission wavelength of 393nm. The potency of inhibitors was measured from the amount of substrate cleavage obtained using a range of test compound concentrations, and, from the resulting dose-response curve, an IC<sub>50</sub> value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

#### Inhibition of MMP-14

##### (i) Enzyme Preparation

Catalytic domain MMP-14 was purchased from Prof. Tschesche, Department of Biochemistry, Faculty of Chemistry, University of Bielefeld, Germany. A 10 M enzyme stock solution was activated for 20 minutes at 25°C following the addition of 5 g/ml of trypsin (Sigma, Dorset, UK). The trypsin activity was then neutralised by the addition of 50 g/ml of soyabean trypsin inhibitor (Sigma, Dorset, UK), prior to dilution of this enzyme stock solution in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM CaCl<sub>2</sub> and 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

##### (ii) Substrate

The fluorogenic substrate used in this screen was Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH<sub>2</sub> (Bachem Ltd, Essex, UK) as described by Will et al (J.Biol.Chem., 271(29), 17119-17123, 1996). The final substrate concentration used in the assay was 10µM.

Determination of enzyme inhibition by test compounds was performed in the same manner as described for MMPs-2 and -9 above.

All references mentioned herein in this text are incorporated by reference in their entirety.

The compounds of the invention are illustrated by the Examples below.

#### EXAMPLES AND PREPARATIONS

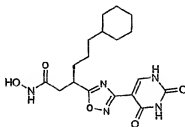
Melting points were determined using open glass capillary tubes and a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data were obtained using Varian Unity Inova-400, Varian Unity Inova-300 or Bruker AC300 spectrometers and are quoted in parts per million from tetramethylsilane. Mass spectral (MS) data were obtained on a Finnigan Mat. TSQ 7000 or a Fisons Instruments Trio 1000. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. Infra red (IR) spectra were measured using a Nicolet Magna 550 Fourier transform infra-red spectrometer. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh, from E. Merck, Darmstadt. Kieselgel 60 F<sub>254</sub> plates from E. Merck were used for TLC, and compounds were visualised using UV light, 5% aqueous potassium permanganate or Dragendorff's reagent (oversprayed with aqueous sodium nitrite). Thermal analyses by Differential Scanning Calorimetry (DSC) and ThermoGravimetric Analysis (TGA) were obtained using Perkin Elmer DSC7 and TGA7. Moisture sorption characteristics were recorded using Surface Measurement Systems Ltd. Automated Water Sorption Analyser DVS 1. Water content was determined on a Mitsubishi CA100 (Coulometric Karl Fisher Titrator). Powder X-ray diffraction (PXRD) pattern was determined using a Siemens D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. Other measurements were taken using standard equipment. Hexane refers to a mixture of hexanes (hplc grade) b.p. 65-70°C. "Ether" and "Et<sub>2</sub>O" refers to diethyl ether. Acetic acid refers to glacial acetic acid. 1-Hydroxy-7-aza-1H-1,2,3-benzotriazole (HOAt). "HOBt" is 1-hydroxy-1H-1,2,3-benzotriazole. N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanilium hexafluorophosphate N-oxide (HATU) and 7-azabenzotriazol-1-ylxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) were purchased from PerSeptive Biosystems U.K. Ltd. "DIPE" refers to diisopropyl ether. Reverse-phase silica gel for flash chromatography was obtained from Fluka (Fluka 100, C<sub>18</sub>, 40-63µm). "DCM" is dichloromethane. "THF" is tetrahydrofuran. "WSCD" is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. EtOAc" is ethyl acetate. "MeOH" is methanol. "DMSO" is dimethylsulphoxide. "ACE-CF" is 1-chloroethyl chloroformate. "NMM" is N-methylmorpholine. "Pentane" refers to High Performance Liquid Chromatography (HPLC) grade n-pentane (b.pt.35-37°C). Nomenclature has been allocated using the commercially available ACD program. Standard abbreviations are used throughout, e.g. "Me" is methyl, "Et" is ethyl, "Pr" is propyl, "Ph" is phenyl, etc.

"HPLC autopurification performed using 2 columns - Phenomenex LUNA C8 150x21.2mm, 10µm and Phenomenex MAGELLEN C18 150x21.2mm, 5µm, eluting with a gradient system of organic solvent [ammonium acetate (aq) 100mM : acetonitrile (1 : 9)] : aqueous solvent [ammonium acetate (aq) 100mM : acetonitrile (9 : 1)]

<sup>b</sup> HPLC autopurification performed using 2 columns - Phenomenex LUNA C8 150x21.2mm, 10 $\mu$ m and Phenomenex MAGELLEN C18 150x21.2mm, 5 $\mu$ m, eluting with a gradient system of organic solvent ( acetonitrile) : aqueous solvent (0.1% aqueous trifluoroacetic acid)

## 5 EXAMPLE 1

(3R)-6-CYCLOHEXYL-3-[3-(2,4-DIOXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINYL)-1,2,4-OXADIAZOL-5-YL]-N-HYDROXYHEXANAMIDE



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To a solution of the title compound from Preparation 3 (0.30 g, 0.8 mmol) in tetrahydrofuran (10 mL) was added triethylamine (0.225 mL, 1.6 mmol). The reaction was cooled to 0 °C in an ice bath, then *iso*-butylchloroformate (0.11 mL, 0.9 mmol) was added and a precipitate began to form immediately. The mixture was stirred for 1 hour, then *O*-trimethylsilyl hydroxylamine (0.32 mL, 2.6 mmol) was added and the reaction was warmed to room temperature and stirred for 2 hours. Methanol (10 mL) was added, stirring was continued for 1 hour and then the solvent was removed *in vacuo*. The residue was partitioned between 2M aqueous hydrochloric acid (20 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (dichloromethane/methanol/acetic acid 90:10:0.5 as eluant) to give the title compound as a white solid (0.19 g).

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Mpt 210 °C.

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<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO)  $\delta$  0.74-0.89 (m, 2H), 1.06-1.24 (m, 8H), 1.53-1.69 (m, 7H), 2.66-2.81 (m, 2H), 3.39-3.47 (m, 1H), 8.05 (s, 1H), 10.9-11.4 (br s, 2H).

LRMS (ES) 414 (M+Na).

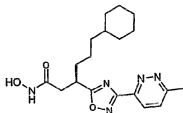
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Anal. Calcd. For  $C_{18}H_{24}N_5O_5 + 1.0 H_2O, 0.1 CH_2Cl_2, 0.1 AcOH$ : C, 51.85; H, 6.56; N, 16.52.  
Found C, 51.79; H, 6.50; N, 16.13.

### EXAMPLE 2

5 (3*R*)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(6-METHYL-3-PYRIDAZINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



To a solution of the title compound from Preparation 6 (0.30 g, 0.9 mmol) in tetrahydrofuran (10 mL) was added triethylamine (0.225 mL, 1.6 mmol). The reaction was cooled to 0 °C in an ice bath, then *iso*-butylchloroformate (0.13 mL, 1.0 mmol) was added and a precipitate began to form immediately. The mixture was stirred for 1 hour, then *O*-trimethylsilyl hydroxylamine (0.32 mL, 2.6 mmol) was added and the reaction was warmed to room temperature and stirred overnight. Methanol (10 mL) was added, stirring was continued for 1 hour and then the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 90:10:0.5 as eluant) to give the title compound as a glassy solid (0.28 g).

20 Mpt 48-55 °C.

<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.75-0.88 (m, 2H), 1.06-1.30 (m, 8H), 1.53-1.77 (m, 7H), 2.42-2.60 (m, 2H), 2.48 (s, 3H), 3.50-3.59 (m, 1H), 8.64 (s, 1H), 8.71 (s, 1H), 9.06 (s, 1H), 10.41 (s, 1H).

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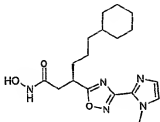
LRMS (ES) 769 (2M+Na), 396 (M+Na), 374 (M+H).

Anal. Calcd. For  $C_{19}H_{27}N_5O_3 + 0.4 H_2O$ : C, 59.95; H, 7.36; N, 18.40. Found C, 59.94; H, 7.64; N, 18.12.

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## EXAMPLE 3

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(1-METHYL-1H-IMIDAZOL-2-YL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



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To a solution of the title compound from Preparation 9 (0.60 g, 1.5 mmol) in tetrahydrofuran (20 mL) was added triethylamine (0.42 mL, 3.0 mmol). The reaction was cooled to 0 °C in an ice bath, then *iso*-butylchloroformate (0.21 mL, 1.65 mmol) was added and a precipitate began to form immediately. The mixture was stirred for 2 hours, then *O*-trimethylsilyl hydroxylamine (0.6 mL, 5.0 mmol) was added and the reaction was warmed to room temperature and stirred overnight. Methanol (10 mL) was added, stirring was continued for 2 hours and then the solvent was removed *in vacuo*. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (dichloromethane/methanol/acetic acid 90:10:1.0 as eluant) to give the title compound as a white foam (0.35 g).

20 Mpt 55-60 °C.

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.77-0.92 (m, 2H), 1.06-1.30 (m, 8H), 1.53-1.77 (m, 7H), 2.40-2.60 (m, 2H), 3.46-3.54 (m, 1H), 3.91 (s, 3H), 7.10 (s, 1H), 7.42 (s, 1H), 8.72 (s, 1H), 10.45 (s, 1H).

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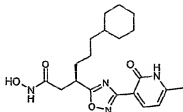
LRMS (ES) 745 (2M+Na), 723 (2M+H), 384 (M+Na), 362 (M+H).

Anal. Calcd. For C<sub>18</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub> + 0.75 H<sub>2</sub>O: C, 57.66; H, 7.36; N, 18.68. Found C, 57.76; H, 7.59; N, 18.83.

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## EXAMPLE 4

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(6-METHYL-2-OXO-1,2-DIHYDRO-3-PYRIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



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To a solution of the title compound from Preparation 12 (0.45 g, 1.2 mmol) in tetrahydrofuran (20 mL) was added triethylamine (0.34 mL, 2.4 mmol). The reaction was cooled to 0 °C in an ice bath, then *iso*-butylchloroformate (0.17 mL, 1.3 mmol) was added and a precipitate began to form immediately. The mixture was stirred for 2 hours, then *O*-trimethylsilyl hydroxylamine (0.48 mL, 4.0 mmol) was added and the reaction was warmed to room temperature and stirred for 4 hours. Methanol (10 mL) was added, stirring was continued for 1 hour and then the solvent was removed *in vacuo*. The residue was partitioned between water (50 mL) and dichloromethane (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), the residue was triturated with hot diisopropyl ether to give the title compound as a white solid (0.42 g).

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Mpt 145-148 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.73-0.86 (m, 2H), 1.25-1.46 (m, 8H), 1.53-1.69 (m, 7H), 2.24 (s, 3H), 2.37-3.55 (m, 2H), 3.40-3.47 (m, 1H), 6.15 (d, 1H), 8.02 (d, 1H), 8.66 (s, 1H), 10.38 (s, 1H), 12.0 (br s, 1H).

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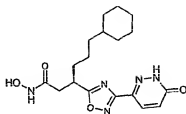
LRMS (ES) 411 (M+Na), 389 (M+H).

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Anal. Calcd. For C<sub>29</sub>H<sub>39</sub>N<sub>4</sub>O<sub>4</sub> + 0.9 H<sub>2</sub>O: C, 59.36; H, 7.42; N, 13.84. Found C, 59.47; H, 7.43; N, 13.73.

**EXAMPLE 5**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(6-OXO-1,6-DIHYDRO-3-PYRIDAZINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



The title compound was obtained as a white solid from the title compound from Preparation 16, using a similar method to that described in Example 3.

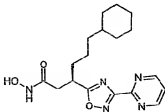
Mpt 174-177 °C

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.76-0.88 (m, 2H), 1.07-1.30 (m, 8H), 1.54-1.75 (m, 7H), 2.41-2.60 (m, 2H), 3.44-3.52 (m, 1H), 7.01 (d, 1H), 7.83 (d, 1H), 8.62 (s, 1H), 10.38 (s, 1H), 13.43 (br s, 1H).

LRMS (ES) 398 (M+Na), 376 (M+H).

**EXAMPLE 6**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(2-PYRIMIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 19, using a similar method to that described in Example 3. The residue was crystallised from

toluene/dichloromethane and then washed with water to remove traces of triethylamine hydrochloride.

Mpt 159-161 °C

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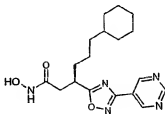
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.75-0.86 (m, 2H), 1.06-1.26 (m, 8H), 1.52-1.65 (m, 5H), 1.52-1.76 (m, 2H), 2.42-2.61 (m, 2H), 3.54-3.60 (m, 1H), 7.67 (dd, 1H), 8.63 (s, 1H), 8.99 (d, 2H), 10.40 (s, 1H).

10 LRMS (ES) 382 (M+Na), 360 (M+H).

Anal. Calcd. For C<sub>18</sub>H<sub>28</sub>N<sub>6</sub>O<sub>3</sub> + 0.2 H<sub>2</sub>O: C, 59.55; H, 7.05; N, 19.29. Found C, 59.70; H, 7.01; N, 18.91.

#### 15 EXAMPLE 7

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(5-PYRIMIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



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The title compound was obtained as a white low melting foam from the title compound of Preparation 22, using a similar method to that described in Example 3. The residue was purified by flash chromatography on silica gel (first column - graded elution of pentane to pentane/ethyl acetate 2:1 to 1:1; second column graded elution dichloromethane to dichloromethane/methanol 98:2 to 95:5; third column ethyl acetate as eluant).

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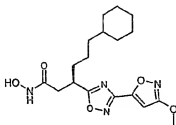
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.72-0.84 (m, 2H), 1.05-1.28 (m, 8H), 1.53-1.72 (m, 7H), 2.44-2.60 (m, 2H), 3.50-3.58 (m, 1H), 8.82 (s, 1H), 9.31 (s, 2H), 9.39 (s, 1H), 10.54 (s, 1H).

30 LRMS (ES) 382 (M+Na), 360 (M+H).

Anal. Calcd. For  $C_{18}H_{25}N_5O_3 + 0.2 \text{ EtOAc}$ : C, 59.89; H, 7.11; N, 18.57. Found C, 60.09; H, 7.13; N, 18.31.

#### EXAMPLE 8

- 5 (3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(3-METHOXY-5-ISOXAZOLYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



- 10 The title compound was obtained as a clear oil from the title compound of Preparation 26, using a similar method to that described in Example 3. The residue was purified by flash chromatography on silica gel (first column - graded elution of dichloromethane to dichloromethane /methanol 98:2 to 95:5; second column - graded elution of pentane/ethyl acetate 2:1 to 1:1 to 100% ethyl acetate).

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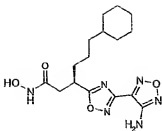
$^1\text{H}$  NMR (400 MHz,  $D_6$ -DMSO)  $\delta$  0.74-0.85 (m, 2H), 1.05-1.27 (m, 8H), 1.55-1.63 (m, 5H), 1.63-1.72 (m, 2H), 2.44-2.59 (m, 2H), 3.47-3.56 (m, 1H), 3.98 (s, 3H), 7.00 (s, 1H), 8.66 (s, 1H), 10.40 (s, 1H).

- 20 LRMS (ES) 401 (M+Na), 379 (M+H).

Anal. Calcd. For  $C_{18}H_{25}N_4O_5 + 0.1 \text{ EtOAc}$ : C, 57.07; H, 6.98; N, 14.47. Found C, 56.87; H, 7.03; N, 14.16.

#### 25 EXAMPLE 9

(3*R*)-3-[3-(4-AMINO-1,2,5-OXADIAZOL-3-YL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYL-*N*-HYDROXYHEXANAMIDE



To a solution of the title compound from Preparation 28 (0.19 g, 0.5 mmol) in dichloromethane (10 mL) was added 1,1-carbonyldiimidazole (0.08 g, 0.5 mmol). The reaction was stirred at room temperature for 1 hour then O-trimethylsilyl hydroxylamine (0.2 mL, 1.5 mmol) was added and the reaction was stirred at room temperature overnight. Methanol (5 mL) was added and stirring was continued for 2 hours. The solvent was removed *in vacuo*, then the residue was dissolved in ethyl acetate (20 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol 90:10) to give the title compound as a white solid (0.11 g).

Mpt 149-152 °C.

<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.77-0.88 (m, 2H), 1.03-1.31 (m, 8H), 1.53-1.67 (m, 5H), 1.67-1.78 (m, 2H), 2.42-2.63 (m, 2H), 3.51-3.60 (m, 1H), 6.34 (s, 2H), 8.67 (s, 1H), 10.42 (s, 1H).

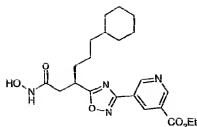
LRMS (ES) 401 (M+Na), 379 (M+H).

HRMS Calcd for C<sub>16</sub>H<sub>24</sub>N<sub>6</sub>O<sub>4</sub> 364.1859. Found 387.1749 (M+Na), 365.1931 (M+H).

#### EXAMPLE 10

ETHYL 5-({(1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL}-1,2,4-OXADIAZOL-3-YL)NICOTINATE

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The title compound was obtained as a pale yellow foam from the title compound of Preparation 31, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (graded elution of  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ , 97.5:2.5:0.25 to 95:5:0.5).

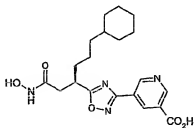
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.75-0.86 (m, 2H), 1.06-1.32 (m, 8H), 1.35 (t, 3H), 1.53-1.66 (m, 5H), 1.66-1.75 (m, 2H), 2.42-2.60 (m, 2H), 3.50-3.58 (m, 1H), 4.40 (q, 2H), 8.65 (s, 1H), 8.70 (s, 1H), 9.22 (s, 2H), 9.35 (s, 1H), 10.40 (s, 1H).

LRMS (ES) 453 (M+Na), 431 (M+H).

Anal. Calcd. For  $C_{22}H_{30}N_4O_5 + 0.2 H_2O$ : C, 60.87; H, 7.06; N, 12.91. Found C, 60.94; H, 7.06; N, 12.98.

### EXAMPLE 11

5-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-  
OXADIAZOL-3-YL)NICOTINIC ACID



To a solution of the title compound of Example 10 (0.41 g, 0.95 mmol) in tetrahydrofuran (5 mL) was added a solution of lithium hydroxide (0.08 g, 1.9 mmol) in water (3 mL) and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was diluted with water (5 mL), acidified to pH1 with 2M aqueous hydrochloric acid and then



extracted with ethyl acetate (2 x 20 mL). The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed *in vacuo* to give a pale orange solid. This was triturated with diisopropylether, the solid was collected by filtration and dried to give the title compound as a white solid (0.22 g).

Mpt 94-96 °C.

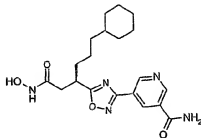
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.75-0.86 (m, 2H), 1.03-1.30 (m, 6H), 1.53-1.64 (m, 5H), 1.64-1.76 (m, 2H), 2.38-2.63 (m, 2H), 3.50-3.60 (m, 1H), 6.65 (br s, 1H), 8.68 (s, 1H), 9.19 (s, 2H), 9.31 (s, 1H), 10.40 (s, 1H).

LRMS (ES) 401 (M-H).

Anal. Calcd. For C<sub>19</sub>H<sub>28</sub>N<sub>4</sub>O<sub>5</sub>: C, 59.03; H, 6.56; N, 13.77. Found C, 58.96; H, 6.64; N, 13.45.

#### EXAMPLE 12

5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)NICOTINAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 34, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 to 85:15:1.5).

Mpt 187-189 °C.

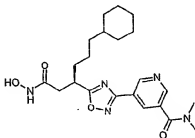
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.70-0.83 (m, 2H), 1.00-1.27 (m, 8H), 1.51-1.62 (m, 5H), 1.62-1.74 (m, 2H), 2.41-2.62 (m, 2H), 3.48-3.57 (m, 1H), 7.78 (s, 1H), 8.40 (s, 1H), 8.71 (s, 1H), 8.82 (s, 1H), 9.18 (s, 1H), 9.25 (s, 1H), 10.55 (s, 1H).

5 LRMS (ES) 400 (M-H).

Anal. Calcd. For C<sub>28</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> + 0.2 H<sub>2</sub>O: C, 59.30; H, 6.82; N, 17.29. Found C, 59.21; H, 6.80; N, 17.28.

#### 10 EXAMPLE 13

5-(5-[(1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL]-1,2,4-OXADIAZOL-3-YL)-*N,N*-DIMETHYLNICOTINAMIDE



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The title compound was obtained as a white foam from the title compound of Preparation 36, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 as eluant).

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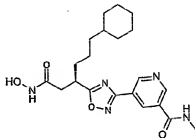
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.75-0.85 (m, 2H), 1.02-1.30 (m, 8H), 1.54-1.64 (m, 5H), 1.64-1.75 (m, 2H), 2.40-2.60 (m, 2H), 2.98 (br d, 6H), 3.49-3.57 (m, 1H), 8.30 (s, 1H), 8.65 (s, 1H), 8.79 (s, 1H), 9.17 (s, 1H), 10.40 (s, 1H).

25 LRMS (ES) 428 (M-H).

Anal. Calcd. For C<sub>22</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub> + 0.35 H<sub>2</sub>O: C, 60.63; H, 7.33; N, 16.07. Found C, 60.34; H, 7.34; N, 16.37.

## EXAMPLE 14

5-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-  
OXADIAZOL-3-YL)-*N*-METHYLNICOTINAMIDE



The title compound was obtained as a white foam from the title compound of Preparation 38, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 as eluant) followed by washing with water.

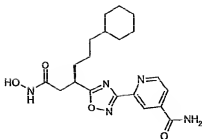
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.75-0.86 (m, 2H), 1.04-1.29 (m, 8H), 1.53-1.65 (m, 5H), 1.65-1.77 (m, 2H), 2.42-2.64 (m, 2H), 2.82 (d, 3H), 3.50-3.57 (m, 1H), 8.65 (s, 2H), 8.73 (s, 1H), 9.14 (s, 1H), 9.20 (s, 1H), 10.40 (s, 1H).

LRMS (ES) 414 (M-H).

Anal. Calcd. For C<sub>21</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub> + 0.25 H<sub>2</sub>O: C, 60.06; H, 7.08 N, 16.67. Found C, 60.00; H, 7.10; N, 16.70.

## EXAMPLE 15

2-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-  
OXADIAZOL-3-YL)ISONICOTINAMIDE



The title compound was obtained as a white foam from the title compound of Preparation 42, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 to 85:15:1.5).

Mpt 165-167 °C.

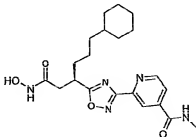
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.74-0.85 (m, 2H), 1.04-1.29 (m, 8H), 1.52-1.64 (m, 5H), 1.64-1.77 (m, 2H), 2.41-2.62 (m, 2H), 3.48-3.57 (m, 1H), 7.73 (s, 1H), 7.95 (d, 1H), 8.35 (s, 1H), 8.40 (s, 1H), 8.69 (s, 1H), 8.87 (d, 1H), 10.43 (s, 1H).

LRMS (ES) 424 (M+Na), 402 (M+H).

Anal. Calcd. For C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> + 0.5 H<sub>2</sub>O: C, 58.52; H, 6.88; N, 17.06. Found C, 58.52; H, 6.80; N, 17.02.

#### EXAMPLE 16

2-(5-((1R)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)-N-METHYLISONICOTINAMIDE



The title compound was obtained as a white foam from the title compound of Preparation 44, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 to 85:15:1.5).

5

Mpt 114-116 °C.

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.74-0.85 (m, 2H), 1.02-1.29 (m, 6H), 1.51-1.64 (m, 5H), 1.64-1.76 (m, 2H), 2.40-2.63 (m, 2H), 2.81 (s, 3H), 3.49-3.57 (m, 1H), 7.90 (d, 1H), 8.37 (s, 1H), 8.65 (s, 1H), 8.80 (s, 1H), 8.87 (d, 1H), 10.41 (s, 1H).

10

LRMS (ES) 438 (M+Na), 416 (M+H).

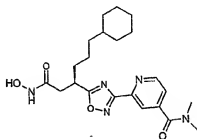
15

Anal. Calcd. For C<sub>27</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub> + 0.3 H<sub>2</sub>O: C, 59.93; H, 7.09; N, 16.64. Found C, 59.96; H, 7.07; N, 16.65.

#### EXAMPLE 17

2-5-((1R)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-  
OXADIAZOL-3-YL)-N,N-DIMETHYLISONICOTINAMIDE

20



25

The title compound was obtained as a white foam from the title compound of Preparation 46, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 to 90:10:1).

Mpt 58-62 °C.

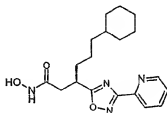
<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.74-0.86 (m, 2H), 1.03-1.29 (m, 8H), 1.53-1.64 (m, 5H), 1.64-1.76 (m, 2H), 2.40-2.63 (m, 2H), 2.90 (s, 3H), 2.99 (s, 3H), 3.49-3.57 (m, 1H), 7.58 (d, 1H), 7.96 (s, 1H), 8.66 (s, 1H), 8.80 (d, 1H), 10.40 (s, 1H).

5 LRMS (ES) 452 (M+Na), 430 (M+H).

Anal. Calcd. For C<sub>22</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub> + 0.4 H<sub>2</sub>O: C, 60.51; H, 7.34; N, 16.04. Found C, 60.49; H, 7.28; N, 15.99.

## 10 EXAMPLE 18

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(2-PYRIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



15

The title compound was obtained as a colourless oil from the title compound of Preparation 48, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 as eluant).

20

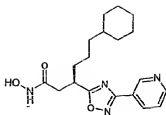
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74-0.89 (m, 2H), 1.03-1.39 (m, 8H), 1.50-1.93 (m, 7H), 2.53-2.92 (m, 2H), 3.67-3.79 (m, 1H), 7.40-7.50 (m, 1H), 7.80-7.88 (m, 1H), 8.10 (d, 1H), 8.77 (d, 1H).

LRMS (ES) 381 (M+Na), 359 (M+H).

25

## EXAMPLE 19

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(3-PYRIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



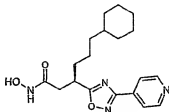
The title compound was obtained as a colourless oil from the title compound of Preparation 50, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 90:10:1 as eluant).

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O-DMSO) δ 0.72-0.85 (m, 2H), 1.01-1.28 (m, 8H), 1.56-1.74 (m, 7H), 2.46-2.62 (m, 2H), 3.48-3.59 (m, 1H), 7.59 (dd, 1H), 8.32 (d, 1H), 8.74-8.81 (m, 2H), 9.16 (d, 1H), 10.52 (s, 1H).

LRMS (ES) 381 (M+Na), 359 (M+H).

#### EXAMPLE 20

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(4-PYRIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



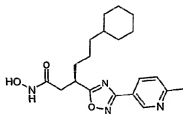
The title compound was obtained as a white solid from the title compound of Preparation 52, using a similar method to that described in Example 9. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 as eluant).

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.74-0.84 (m, 2H), 1.02-1.28 (m, 8H), 1.55-1.66 (m, 5H), 1.66-1.74 (m, 2H), 2.43-2.61 (m, 2H), 3.48-3.58 (m, 1H), 7.90 (d, 2H), 8.76-8.82 (m, 3H), 10.52 (s, 1H).

LRMS (ES) 381 (M+Na), 359 (M+H).

#### EXAMPLE 21

- 5 (3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(6-METHYL-3-PYRIDINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



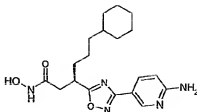
- 10 The title compound was obtained as a white solid from the title compound of Preparation 55, using a similar method to that described in Example 9. The residue was purified by preparative hplc.

- <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.91 (m, 2H), 1.10-1.40 (m, 8H), 1.58-1.74 (m, 5H), 1.74-1.88 (m, 2H), 2.59 (dd, 1H), 2.62 (s, 3H), 2.70 (dd, 1H), 3.59-3.66 (m, 1H), 7.46 (d, 1H), 8.31 (d, 1H), 9.05 (s, 1H).

LRMS (ES) 395 (M+Na), 373 (M+H).

#### 20 EXAMPLE 22

(3R)-3-[3-(6-AMINO-3-PYRIDINYL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYL-N-HYDROXYHEXANAMIDE





To a solution of the title compound from Preparation 59 (0.21 g, 0.6 mmol) in dichloromethane (20 mL) was added *N*-methylmorpholine (0.07 mL, 0.66 mmol). The reaction was cooled to 0 °C in an ice bath, then *iso*-butylchloroformate (0.09 mL, 0.66 mmol) was added. The mixture was stirred for 1 hour, then *O*-trimethylsilyl hydroxylamine (0.48 mL, 4.0 mmol) was added and the reaction was warmed to room temperature and stirred for 1 hour. Methanol (10 mL) was added, stirring was continued for 20 minutes and then the solvent was removed *in vacuo*. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was purified by preparative hplc to give the title compound as a white solid (0.06 g).

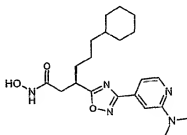
Mpt 168-170 °C

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.92 (m, 2H), 1.11-1.37 (m, 8H), 1.60-1.74 (m, 5H), 1.74-1.84 (m, 2H), 2.57 (dd, 1H), 2.68 (dd, 1H), 3.56-3.62 (m, 1H), 6.65 (d, 1H), 8.00 (d, 1H), 8.57 (s, 1H).

LRMS (ES) 396 (M+Na), 374 (M+H).

#### EXAMPLE 23

(3*R*)-6-CYCLOHEXYL-3-[3-[2-(DIMETHYLAMINO)-4-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL]-*N*-HYDROXYHEXANAMIDE



To a solution of the title compound from Preparation 62 (0.32 g, 0.64 mmol) in tetrahydrofuran (10 mL) was added triethylamine (0.9 mL, 0.64 mmol) followed by 1,1-carboxyldiimidazole (0.10 g, 0.64 mmol). The mixture was stirred at room temperature for 2 hours, then hydroxylamine hydrochloride (0.04 g, 0.64 mmol) was added and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was washed with brine, then dried

(MgSO<sub>4</sub>) and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol/aqueous ammonia solution 95:5:0.5 to 80:20:3) to give the title compound as a yellow oil (0.05 g).

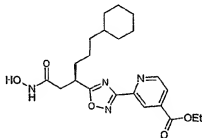
- 5 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.92 (m, 2H), 1.11-1.40 (m, 8H), 1.59-1.72 (m, 5H), 1.76-1.85 (m, 2H), 2.58 (dd, 1H), 2.69 (dd, 1H), 3.15 (s, 3H), 3.60-3.66 (m, 1H), 7.16 (d, 1H), 7.25 (s, 1H), 8.19 (6, 1H).

LRMS (TSP) 401 (M+H).

10

#### EXAMPLE 24

ETHYL 2-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)ISONICOTINATE



15

The title compound was obtained as a colourless oil from the title compound of Preparation 63, using a similar method to that described in Example 22.

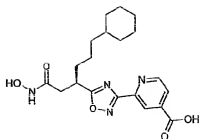
- 20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.75-0.89 (m, 2H), 1.11-1.40 (m, 8H), 1.45 (t, 3H), 1.53-1.97 (m, 7H), 2.68 (dd, 1H), 2.84 (dd, 1H), 3.67-3.79 (m, 1H), 4.48 (q, 2H), 7.98 (d, 1H), 8.61 (s, 1H), 8.90 (d, 1H).

LRMS (ES) 453 (M+Na), 431 (M+H).

25

#### EXAMPLE 25

2-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)ISONICOTINIC ACID



To a solution of the title compound of Example 24 (0.44 g, 1.0 mmol) in methanol (20 mL) was added a solution of lithium hydroxide (0.09 g, 2.0 mmol) in water (7 mL) and the reaction was stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the residue was diluted with water (20 mL) and dichloromethane (20 mL). The layers were separated, the organic layer was discarded and the aqueous layer was acidified to pH4 with 2M aqueous hydrochloric acid and then extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo* to give the title compound as a white solid (0.04 g).

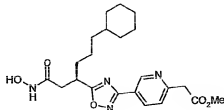
Mpt 117-122 °C.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.80-0.93 (m, 2H), 1.06-1.47 (m, 8H), 1.53-1.75 (m, 5H), 1.75-1.93 (m, 2H), 2.62 (dd, 1H), 2.74 (dd, 1H), 3.62-3.73 (m, 1H), 8.07 (d, 1H), 8.62 (s, 1H), 8.89 (d, 1H).

LRMS (TSP) 403 (M).

## 20 EXAMPLE 26

METHYL [5-((5-((1*R*)-4-CYCLOHEXYL-1-[2-((HYDROXYAMINO)-2-OXOETHYL)BUTYL]-1,2,4-OXADIAZOL-3-YL)-2-PYRIDINYL]ACETATE



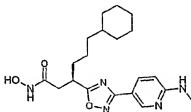
The title compound was obtained as a pale yellow solid from the title compound of Preparation 67', using a similar method to that described in Example 22'.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.80-0.94 (m, 2H), 1.08-1.42 (m, 8H), 1.55-1.75 (m, 5H), 1.75-1.88 (m, 2H), 2.60 (dd, 1H), 2.72 (dd, 1H), 3.59-3.69 (m, 1H), 3.73 (s, 3H), 3.97 (s, 2H), 7.58 (d, 1H), 8.40 (d, 1H), 9.12 (s, 1H).

LRMS (ES) 453 (M+Na), 431 (M+H).

#### 10 EXAMPLE 27'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-[6-(METHYLAMINO)-3-PYRIDINYL]-1,2,4-  
OXADIAZOL-5-YL]HEXANAMIDE



15

To a solution of the title compound from Preparation 71' (0.24 g, 0.65 mmol) in tetrahydrofuran (7 mL) was added 1,1-carbonyldiimidazole (0.12 g, 0.72 mmol). The reaction was stirred at room temperature for 1 hour then O-trimethylsilyl hydroxylamine (0.24 mL, 2.0 mmol) was added and the reaction was stirred at room temperature for 48 hours. 10% aqueous citric acid solution (10 mL) was added and stirring was continued for 1.5 hours. The mixture was diluted with ethyl acetate (20 mL) and water (20 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (20 mL), saturated aqueous sodium dihydrogen citrate solution (20 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was purified by preparative hplc, with the title compound being isolate as a white solid (0.07 g) after freeze-drying.

20

25

Mpt 127-129 °C.

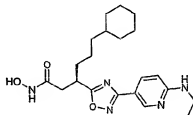
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.78-0.90 (m, 2H), 1.09-1.37 (m, 8H), 1.58-1.72 (m, 5H), 1.72-1.82 (m, 2H), 2.56 (dd, 1H), 2.67 (dd, 1H), 2.90 (s, 3H), 3.54-3.61 (m, 1H), 6.58 (d, 1H), 7.95 (dd, 1H), 8.61 (d, 1H).

5 LRMS (ES) 388 (M+H).

#### EXAMPLE 28'

(3R)-6-CYCLOHEXYL-3-{3-[6-(ETHYLAMINO)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL}-N-HYDROXYHEXANAMIDE

10



The title compound was obtained as a white solid from the title compound of Preparation 72', using a similar method to that described in Example 27'.

15

Mpt 146-148 °C.

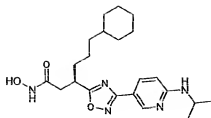
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.79-0.93 (m, 2H), 1.08-1.40 (m, 11H), 1.59-1.82 (m, 7H), 2.56 (dd, 1H), 2.67 (dd, 1H), 3.37 (q, 2H), 3.52-3.62 (m, 1H), 6.59 (d, 1H), 7.94 (dd, 1H), 8.60 (d, 1H).

20

LRMS (ES) 402 (M+H).

#### EXAMPLE 29'

25 (3R)-6-CYCLOHEXYL-N-HYDROXY-3-{3-[6-(ISOPROPYLAMINO)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL}HEXANAMIDE



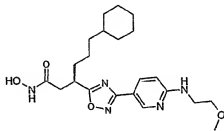
The title compound was obtained as a colourless oil from the title compound of Preparation 73', using a similar method to that described in Example 22'.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.80-0.94 (m, 2H), 1.08-1.38 (m, 14H), 1.60-1.82 (m, 7H), 2.55 (dd, 1H), 2.68 (dd, 1H), 3.53-3.63 (m, 1H), 4.02-4.12 (m, 1H), 6.58 (d, 1H), 7.93 (dd, 1H), 8.60 (d, 1H).

LRMS (ES) 416 (M+H).

#### EXAMPLE 30'

(3*R*)-6-CYCLOHEXYL-N-HYDROXY-3-(3-{6-[(2-METHOXYETHYL)AMINO]-3-PYRIDINYL}-1,2,4-OXADIAZOL-5-YL)HEXANAMIDE



To a solution of the title compound from Preparation 74' (0.08 g, 0.2 mmol) in tetrahydrofuran (3 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.04 g, 0.22 mmol), triethylamine (0.03 mL, 0.22 mmol) and O-trimethylsilyl hydroxylamine (0.03 mL, 0.22 mmol) and the reaction was stirred at room temperature for 5 hours. Further amounts of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.02 g, 0.11 mmol) and O-trimethylsilyl hydroxylamine (0.015 mL, 0.11 mmol) were added and the reaction was continued at room temperature for 24 hours. 1M aqueous citric acid solution (10 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was purified by reverse phase hplc

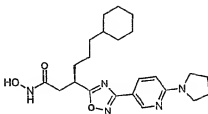
(acetonitrile/0.1M aqueous ammonium acetate solution as eluant) to give the title compound as a white solid (0.02 g) after freeze drying.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.77-0.91 (m, 2H), 1.06-1.40 (m, 8H), 1.55-1.76 (m, 7H), 2.61-2.71 (m, 2H), 3.28-3.46 (m, 5H), 3.55-3.70 (m, 3H), 6.15 (br s, 1H), 6.33 (d, 1H), 7.81 (d, 1H), 8.35 (s, 1H).

LRMS (ES) 432 (M+H).

#### 10 EXAMPLE 31'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-[6-(1-PYRROLIDINYL)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



15

The title compound was obtained as a white solid from the title compound of Preparation 75', using a similar method to that described in Example 27'.

Mpt 137-145 °C.

20

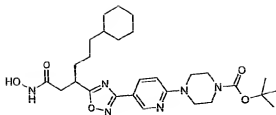
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.80-0.91 (m, 2H), 1.09-1.36 (m, 8H), 1.59-1.72 (m, 5H), 1.72-1.81 (m, 2H), 1.99-2.08 (m, 4H), 2.56 (dd, 1H), 2.67 (dd, 1H), 3.44-3.54 (m, 4H), 3.54-3.65 (m, 1H), 6.60 (d, 1H), 8.06 (dd, 1H), 8.68 (d, 1H).

25 LRMS (ES) 428 (M+H).

#### EXAMPLE 32'

TERT-BUTYL 4-[5-[5-[(1R)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL]-1,2,4-OXADIAZOL-3-YL]-2-PYRIDINYL]-1-PIPERAZINECARBOXYLATE

30



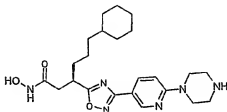
The title compound was obtained as a colourless oil from the title compound of Preparation 76', using a similar method to that described in Example 22'.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.75-0.93 (m, 2H), 1.00-1.35 (m, 8H), 1.45 (s, 9H), 1.50-1.66 (m, 5H), 1.66-1.82 (m, 2H), 2.50-2.60 (m, 1H), 2.60-2.78 (m, 1H), 3.44-3.66 (m, 9H), 6.59 (d, 1H), 7.98 (d, 1H), 8.74 (s, 1H).

LRMS (ES) 543 (M+H).

#### EXAMPLE 33'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-{3-[6-(1-PIPERAZINYL)-3-PYRIDINYL]-1,2,4-  
OXADIAZOL-5-YL}HEXANAMIDE



To a solution of the title compound from Example 32' (0.37 g, 0.7 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL) and the reaction was stirred at room temperature for 1.5 hours. The solvent was removed in vacuo and the residue was azeotroped with toluene. The residue was then dissolved in ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL) followed by 10% aqueous citric acid solution (30 mL). The acidic aqueous layer was basified to pH7 with saturated aqueous sodium bicarbonate solution and then extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water (30 mL), dried (MgSO<sub>4</sub>) and the solvent was removed in vacuo to give the title compound as a viscous oil (0.03 g).



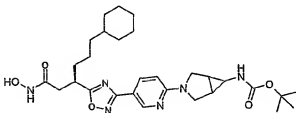
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.80-0.91 (m, 2H), 1.05-1.40 (m, 8H), 1.53-1.70 (m, 5H), 1.70-1.84 (m, 2H), 2.54 (dd, 1H), 2.66 (dd, 1H), 2.88-2.96 (m, 4H), 3.50-3.62 (m, 5H), 6.87 (d, 1H), 8.06 (d, 1H), 8.70 (s, 1H).

5 LRMS (ES) 443 (M+H).

#### EXAMPLE 34'

*TERT*-BUTYL 3-[5-{5-[(1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL]-1,2,4-OXADIAZOL-3-YL}-2-PYRIDINYL]-3-AZABICYCLO[3.1.0]HEX-6-YLCARBAMATE

10



The title compound was obtained as a yellow oil from the title compound of Preparation 77', using a similar method to that described in Example 22'.

15

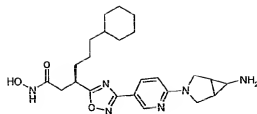
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.95 (m, 2H), 1.07-1.70 (m, 24H), 1.70-1.90 (m, 2H), 2.60 (dd, 1H), 2.88-3.01 (m, 1H), 3.50-3.61 (m, 3H), 3.79-3.88 (m, 2H), 4.74 (s, 1H), 6.33 (d, 1H), 7.97 (d, 1H), 8.75 (s, 1H).

20 LRMS (ES) 555 (M+H).

#### EXAMPLE 35'

(3*R*)-3-[3-[6-(6-AMINO-3-AZABICYCLO[3.1.0]HEX-3-YL)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYL-*N*-HYDROXYHEXANAMIDE

25



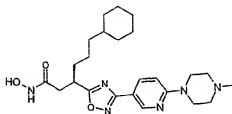
The title compound was obtained as a yellow oil from the title compound of Example 34', using a similar method to that described in Example 33'.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.78-1.00 (m, 2H), 1.07-1.70 (m, 9H), 1.54-1.87 (m, 8H), 2.54 (dd, 1H), 2.66 (dd, 1H), 3.45-3.63 (m, 3H), 3.67-3.76 (m, 2H), 6.54 (d, 1H), 8.05 (d, 1H), 8.66 (s, 1H).

LRMS (ES) 455 (M+H).

#### EXAMPLE 36'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-[6-(4-METHYL-1-PIPERAZINYL)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



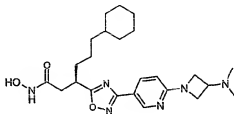
The title compound was obtained as a brown oil from the title compound of Preparation 79', using a similar method to that described in Example 22'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.80-0.91 (m, 2H), 1.08-1.39 (m, 8H), 1.56-1.72 (m, 5H), 1.72-1.83 (m, 2H), 2.39 (s, 3H), 2.52-2.63 (m, 5H), 2.67 (dd, 1H), 3.55-3.62 (m, 1H), 3.68-3.74 (m, 4H), 6.90 (d, 1H), 8.09 (dd, 1H), 8.74 (d, 1H).

LRMS (TSP) 455 (M).

**EXAMPLE 37'**

(3*R*)-6-CYCLOHEXYL-3-(3-[6-[3-(DIMETHYLAMINO)-1-AZETIDINYL]-3-PYRIDINYL]-1,2,4-  
OXADIAZOL-5-YL)-*N*-HYDROXYHEXANAMIDE



5

The title compound was obtained as a white solid from the title compound of Preparation 81', using a similar method to that described in Example 22'.

10 Mpt 136-137 °C.

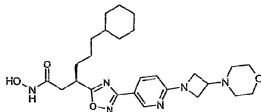
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.79-0.92 (m, 2H), 1.11-1.39 (m, 8H), 1.57-1.72 (m, 5H), 1.72-1.86 (m, 2H), 2.25 (s, 6H), 2.54 (dd, 1H), 2.67 (dd, 1H), 3.28-3.36 (m, 1H), 3.54-3.61 (m, 1H), 3.89-3.97 (m, 2H), 4.15-4.20 (m, 2H), 6.50 (d, 1H), 8.07 (dd, 1H), 8.67 (d, 1H).

15

LRMS (ES) 457 (M+H).

**EXAMPLE 38'**

20 (3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-(3-[6-[3-(4-MORPHOLINYL)-1-AZETIDINYL]-3-PYRIDINYL]-1,2,4-  
OXADIAZOL-5-YL)HEXANAMIDE



25 The title compound was obtained as a white solid from the title compound of Preparation 83', using a similar method to that described in Example 22'.

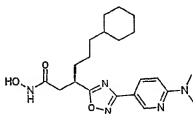
Mpt 151-153 °C.

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O-DMSO) δ 0.70-0.88 (m, 2H), 1.00-1.36 (m, 8H), 1.47-1.79 (m, 7H), 2.25-2.43 (m, 4H), 2.43-2.62 (m, 2H), 3.20-3.63 (m, 2H), 3.51-3.63 (m, 4H), 3.80-3.91 (m, 2H), 3.98-4.11 (m, 2H), 6.49 (d, 1H), 7.98 (dd, 1H), 8.62 (d, 1H), 8.80 (s, 1H), 10.50 (s, 1H).

LRMS (ES) 499 (M+H).

#### 10 EXAMPLE 39'

(3*R*)-6-CYCLOHEXYL-3-[3-[6-(DIMETHYLAMINO)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL]-*N*-HYDROXYHEXANAMIDE



15

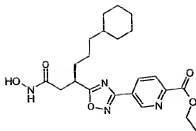
The title compound was obtained as a colourless glass from the title compound of Preparation 85', using a similar method to that described in Example 22', apart from the use of dimethylformamide as the reaction solvent.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.72-0.88 (m, 2H), 1.03-1.36 (m, 8H), 1.45-1.82 (m, 7H), 2.58 (dd, 1H), 2.72 (dd, 1H), 3.13 (s, 6H), 3.54-3.64 (m, 1H), 6.49 (d, 1H), 7.92 (d, 1H), 8.71 (s, 1H).

LRMS (ES) 402 (M+H).

#### 25 EXAMPLE 40'

ETHYL 5-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)-2-PYRIDINECARBOXYLATE



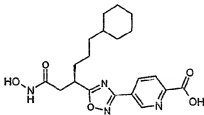
The title compound was obtained as a white foam from the title compound of Preparation 87', using a similar method to that described in Example 9'. The compound was purified by preparative hplc.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.72-0.90 (m, 2H), 1.02-1.35 (m, 8H), 1.46 (t, 3H), 1.54-1.70 (m, 5H), 1.70-1.87 (m, 2H), 2.64 (dd, 1H), 2.78 (dd, 1H), 3.61-3.72 (m, 1H), 4.49 (q, 2H), 8.18 (d, 1H), 8.40 (d, 1H), 9.29 (s, 1H).

LRMS (ES) 883 (2M+Na), 453 (M+Na), 431 (M+H).

#### EXAMPLE 41'

5-(5-((1R)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-  
OXADIAZOL-3-YL)-2-PYRIDINECARBOXYLIC ACID



The title compound was obtained as a white solid from the title compound of Example 41', using a similar method to that described in Example 25'. The compound was purified by preparative hplc.

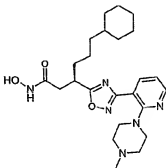
Mpt 168-170 °C.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.78-0.96 (m, 2H), 1.08-1.42 (m, 8H), 1.57-1.88 (m, 7H), 2.51-2.80 (m, 2H), 3.57-3.72 (m, 1H), 8.29 (d, 1H), 8.60 (d, 1H), 9.30 (s, 1H).

LRMS (TSP) 403 (M+H).

**EXAMPLE 42'**

- 5 (3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-{3-[2-(4-METHYL-1-PIPERAZINYL)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL}HEXANAMIDE



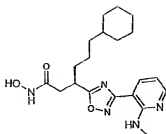
- 10 The title compound was obtained as a colourless oil from the title compound of Preparation 90', using a similar method to that described in Example 22'.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74-0.92 (m, 2H), 1.01-1.42 (m, 8H), 1.52-1.90 (m, 7H), 2.40 (s, 3H), 2.56-2.80 (m, 6H), 3.14-3.27 (m, 2H), 3.45-3.72 (m, 3H), 6.83 (dd, 1H), 7.00-7.80 (br, 2H),  
15 7.88 (d, 1H), 8.29 (d, 1H).

LRMS (ES) 457 (M+H).

**EXAMPLE 43'**

- 20 (3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-{3-[2-(METHYLAMINO)-3-PYRIDINYL]-1,2,4-OXADIAZOL-5-YL}HEXANAMIDE



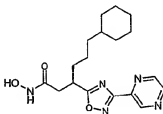
The title compound was obtained as a pale yellow oil from the title compound of Preparation 91', using a similar method to that described in Example 22'.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.80-0.94 (m, 2H), 1.08-1.39 (m, 8H), 1.60-1.75 (m, 5H), 1.75-1.86 (m, 2H), 2.60 (dd, 1H), 2.71 (dd, 1H), 3.58-3.68 (m, 1H), 6.72 (dd, 1H), 8.21 (d, 1H), 8.33 (d, 1H).

LRMS (ES) 371 (M).

#### EXAMPLE 44'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(2-PYRAZINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 93', using a similar method to that described in Example 23'.

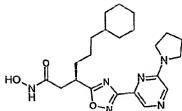
Mpt 124-125 °C.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.93 (m, 2H), 1.10-1.43 (m, 8H), 1.58-1.75 (m, 5H), 1.75-1.92 (m, 2H), 2.61 (dd, 1H), 2.73 (dd, 1H), 3.53-3.62 (m, 1H), 8.75-8.80 (m, 2H), 9.32 (s, 1H).

LRMS (TSP) 360 (M+H).

#### EXAMPLE 45'

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-[6-(1-PYRROLIDINYL)-2-PYRAZINYL]-1,2,4-  
5 OXADIAZOL-5-YL]HEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 95',  
10 using a similar method to that described in Example 23'.

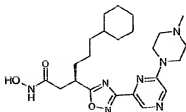
Mpt 124-125 °C.

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 0.75-0.96 (m, 2H), 1.03-1.30 (m, 6H), 1.50-1.74 (m, 7H), 1.93-  
15 2.00 (m, 4H), 2.58-2.80 (m, 2H), 3.43-3.56 (m, 5H), 8.13 (s, 1H), 8.30 (s, 1H), 8.78 (s, 1H),  
10.50 (s, 1H).

LRMS (ES) 451 (M+Na), 429 (M+H).

#### EXAMPLE 46'

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-[6-(4-METHYL-1-PIPERAZINYL)-2-PYRAZINYL]-  
1,2,4-OXADIAZOL-5-YL]HEXANAMIDE





The title compound was obtained as a white foam from the title compound of Preparation 98', using a similar method to that described in Example 9'. The compound was purified by preparative hplc.

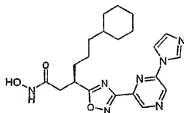
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.93 (m, 2H), 1.08-1.40 (m, 8H), 1.50-1.74 (m, 5H), 1.75-1.85 (m, 2H), 2.40 (s, 3H), 2.56-2.77 (m, 6H), 3.60-3.67 (m, 1H), 3.76-3.82 (m, 4H), 8.38 (s, 1H), 8.47 (s, 1H).

LRMS (ES) 480 (M+Na), 458 (M+H).

10

**EXAMPLE 47'**

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-{3-[6-(1H-IMIDAZOL-1-YL)-2-PYRAZINYL]-1,2,4-OXADIAZOL-5-YL}HEXANAMIDE



15

The title compound was obtained as a white solid from the title compound of Preparation 100', using a similar method to that described in Example 9'. The product was recrystallised from methanol.

20

Mpt 162 °C.

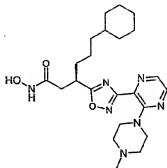
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.92 (m, 2H), 1.08-1.40 (m, 8H), 1.60-1.73 (m, 5H), 1.77-1.90 (m, 2H), 2.64 (dd, 1H), 2.75 (dd, 1H), 3.63-3.73 (m, 1H), 7.23 (s, 1H), 8.12 (s, 1H), 8.78 (s, 1H), 9.24 (s, 1H), 9.26 (s, 1H).

25

LRMS (ES) 448 (M+Na), 426 (M+H).

**EXAMPLE 48'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-[3-(4-METHYL-1-PIPERAZINYL)-2-PYRAZINYL]-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



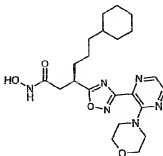
The title compound was obtained as a white foam from the title compound of Preparation 104', using a similar method to that described in Example 9'. The product was purified by preparative hplc.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.92 (m, 2H), 1.08-1.40 (m, 8H), 1.60-1.73 (m, 5H), 1.77-1.90 (m, 2H), 2.45 (s, 3H), 2.64 (dd, 1H), 2.70-2.80 (m, 5H), 3.30-3.50 (m, 4H), 3.63-3.73 (m, 1H), 8.12 (s, 1H), 8.40 (s, 1H).

LRMS (ES) 458 (M+H).

**EXAMPLE 49'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-[3-(4-MORPHOLINYL)-2-PYRAZINYL]-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



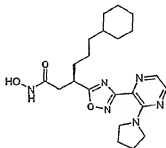
The title compound was obtained as a yellow foam from the title compound of Preparation 108', using a similar method to that described in Example 23'. The product was purified by preparative hplc.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.81-0.93 (m, 2H), 1.13-1.38 (m, 8H), 1.58-1.74 (m, 5H), 1.74-1.86 (m, 2H), 2.61 (dd, 1H), 2.70 (dd, 1H), 3.26-3.35 (m, 4H), 3.58-3.68 (m, 1H), 3.68-3.79 (m, 4H), 8.14 (s, 1H), 8.32 (s, 1H).

LRMS (ES) 467 (M+Na), 445 (M+H).

#### EXAMPLE 50'

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-(3-[3-(1-PYRROLIDINYL)-2-PYRAZINYL]-1,2,4-OXADIAZOL-5-YL)HEXANAMIDE



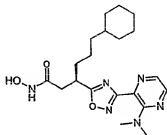
The title compound was obtained as a white foam from the title compound of Preparation 112', using a similar method to that described in Example 23'. The product was purified by preparative hplc.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.93 (m, 2H), 1.08-1.38 (m, 8H), 1.58-1.74 (m, 5H), 1.74-1.85 (m, 2H), 1.85-1.94 (m, 4H), 2.58 (dd, 1H), 2.67 (dd, 1H), 3.25-3.34 (m, 4H), 3.61-3.68 (m, 1H), 7.90 (d, 1H), 8.20 (d, 1H).

LRMS (ES) 451 (M+Na), 428 (M+H).

**EXAMPLE 51'**

(3*R*)-6-CYCLOHEXYL-3-[3-(3-(DIMETHYLAMINO)-2-PYRAZINYL)-1,2,4-OXADIAZOL-5-YL]-*N*-HYDROXYHEXANAMIDE



5

The title compound was obtained as a white foam from the title compound of Preparation 116', using a similar method to that described in Example 23'. The product was purified by preparative hplc.

10

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.93 (m, 2H), 1.10-1.38 (m, 8H), 1.58-1.74 (m, 5H), 1.74-1.85 (m, 2H), 2.58 (dd, 1H), 2.70 (dd, 1H), 2.93 (s, 6H), 3.59-3.67 (m, 1H), 7.98 (d, 1H), 8.21 (d, 1H).

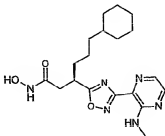
15

LRMS (ES) 425 (M+Na), 403 (M+H).

**EXAMPLE 52'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-[3-(METHYLAMINO)-2-PYRAZINYL]-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE

20



The title compound was obtained as a white solid from the title compound of Preparation 119', using a similar method to that described in Example 23'. The product was purified by preparative hplc.

5 Mpt 115-120 °C.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.92 (m, 2H), 1.10-1.42 (m, 8H), 1.57-1.74 (m, 5H), 1.74-1.87 (m, 2H), 2.60 (dd, 1H), 2.72 (dd, 1H), 3.11 (d, 3H), 3.61-3.70 (m, 1H), 7.41 (br s, 1H), 7.92 (d, 1H), 8.25 (d, 1H).

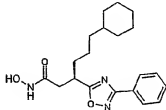
10

LRMS (ES) 411 (M+Na), 389 (M+H).

Anal. Calcd. For C<sub>19</sub>H<sub>26</sub>N<sub>6</sub>O<sub>5</sub>: C, 58.75; H, 7.27; N, 21.63. Found C, 58.68; H, 7.30; N, 21.49.

# 15 EXAMPLE 53'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-(3-PHENYL-1,2,4-OXADIAZOL-5-YL)HEXANAMIDE



20 The title compound was obtained as a colourless oil from the title compound of Preparation 121', using a similar method to that described in Example 23'.

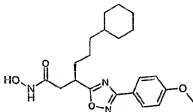
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.06-1.38 (m, 8H), 1.58-1.84 (m, 7H), 2.50-2.62 (m, 1H), 2.62-2.77 (m, 1H), 3.55-3.63 (m, 1H), 7.40-7.51 (m, 3H), 7.97-8.06 (m, 2H).

25

LRMS (TSP) 380 (M+Na), 358 (M+H).

**EXAMPLE 54'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(4-METHOXYPHENYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



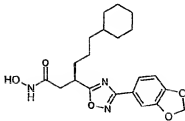
The title compound was obtained as a colourless oil from the title compound of Preparation 123', using a similar method to that described in Example 22'.

- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.92 (m, 2H), 1.10-1.38 (m, 8H), 1.59-1.72 (m, 5H), 1.72-1.84 (m, 2H), 2.56 (dd, 1H), 2.70 (dd, 1H), 3.56-3.63 (m, 1H), 3.86 (s, 3H), 7.03 (d, 2H), 7.97 (d, 2H).

LRMS (TSP) 388 (M+H).

**EXAMPLE 55'**

(3*R*)-3-[3-(1,3-BENZODIOXOL-5-YL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYL-*N*-HYDROXYHEXANAMIDE



The title compound was obtained as a colourless oil from the title compound of Preparation 125', using a similar method to that described in Example 23'.

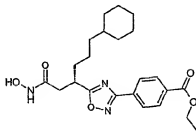
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.75-0.90 (m, 2H), 1.05-1.37 (m, 8H), 1.58-1.83 (m, 7H), 2.49-2.61 (m, 1H), 2.61-2.74 (m, 1H), 3.53-3.63 (m, 1H), 6.01 (s, 2H), 6.87 (d, 1H), 7.45 (s, 1H), 7.57 (d, 1H).

5 LRMS (TSP) 402 (M+H).

#### EXAMPLE 56'

ETHYL 4-(5-((1R)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)BENZOATE

10



The title compound was obtained as a colourless foam from the title compound of Preparation 127', using a similar method to that described in Example 22'.

15

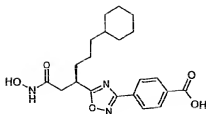
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.80-0.94 (m, 2H), 1.10-1.48 (m, 11H), 1.57-1.74 (m, 5H), 1.74-1.88 (m, 2H), 2.59 (dd, 1H), 2.70 (dd, 1H), 3.59-3.68 (m, 1H), 4.40 (q, 2H), 8.17 (s, 4H).

LRMS (TSP) 429 (M).

20

#### EXAMPLE 57'

4-(5-((1R)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)BENZOIC ACID



The title compound was obtained as a white solid from the title compound of Example 56', using a similar method to that described in Example 25'. The compound was purified by preparative hplc.

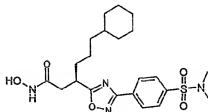
Mpt 142-146 °C.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.78-0.92 (m, 2H), 1.10-1.38 (m, 8H), 1.58-1.72 (m, 5H), 1.72-1.88 (m, 2H), 2.54-2.62 (m, 1H), 2.62-2.76 (m, 1H), 3.57-3.67 (m, 1H), 8.10-8.17 (m, 4H).

LRMS (TSP) 429 (M).

#### EXAMPLE 58'

(3R)-6-CYCLOHEXYL-3-(3-{4-[(DIMETHYLAMINO)SULFONYL]PHENYL}-1,2,4-OXADIAZOL-5-YL)-N-HYDROXYHEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 131', using a similar method to that described in Example 22'.

Mpt 52-60 °C.

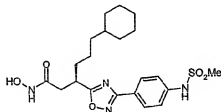
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.78-0.93 (m, 2H), 1.08-1.40 (m, 8H), 1.58-1.73 (m, 5H), 1.73-1.88 (m, 2H), 2.59 (dd, 1H), 2.65-2.77 (m, 7H), 3.59-3.70 (m, 1H), 7.94 (d, 2H), 8.29 (d, 2H).



LRMS (TSP) 464 (M).

**EXAMPLE 59'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-(3-{4-[(METHYLSULFONYL)AMINO]PHENYL}-1,2,4-  
5 OXADIAZOL-5-YL)HEXANAMIDE



The title compound was obtained as a white foam from the title compound of Preparation 133',  
10 using a similar method to that described in Example 22'.

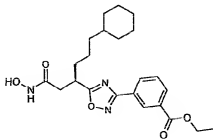
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.92 (m, 2H), 1.00-1.40 (m, 8H), 1.58-1.92 (m, 7H), 2.64 (dd, .  
1H), 2.79 (dd, 1H), 3.01 (s, 3H), 3.55-3.66 (m, 1H), 7.20 (d, 2H), 7.67 (br s, 1H), 7.87 (d, 2H),  
8.94 (br s, 1H).

15

LRMS (ES) 473 (M+Na), 451 (M+H).

**EXAMPLE 60'**

ETHYL 3-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-  
20 OXADIAZOL-3-YL)BENZOATE



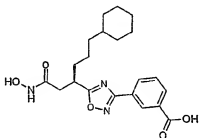
The title compound was obtained as a brown foam from the title compound of Preparation 136', using a similar method to that described in Example 22'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.91 (m, 2H), 1.03-1.48 (m, 11H), 1.54-1.92 (m, 7H), 2.63 (dd, 1H), 2.80 (dd, 1H), 3.61-3.22 (m, 1H), 4.42 (q, 2H), 7.55 (dd, 1H), 8.17 (d, 1H), 8.21 (d, 1H), 8.66 (s, 1H).

LRMS (TSP) 430 (M+H).

#### 10 EXAMPLE 61'

3-(5-((1*R*)-4-CYCLOHEXYL-1-[2-(HYDROXYAMINO)-2-OXOETHYL]BUTYL)-1,2,4-OXADIAZOL-3-YL)BENZOIC ACID



15

The title compound was obtained as a white solid from the title compound of Example 60', using a similar method to that described in Example 25'. The reaction was carried out at 70 °C and the product was purified by preparative hplc.

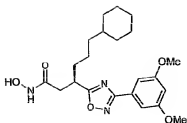
20 <sup>1</sup>H NMR (300 MHz, D<sub>6</sub>-DMSO) δ 0.72-0.87 (m, 2H), 1.00-1.36 (m, 8H), 1.47-1.90 (m, 7H), 2.43-2.63 (m, 2H), 3.45-3.58 (m, 1H), 7.70 (dd, 1H), 8.14 (d, 1H), 8.21 (d, 1H), 8.54 (s, 1H), 8.79 (br s, 1H), 10.50 (s, 1H), 13.30 (br s, 1H).

LRMS (ES) 402 (M+H).

25

#### EXAMPLE 62'

(3*R*)-6-CYCLOHEXYL-3-[3-(3,5-DIMETHOXYPHENYL)-1,2,4-OXADIAZOL-5-YL]-*N*-HYDROXYHEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 138', using a similar method to that described in Example 23'.

5

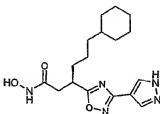
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.92 (m, 2H), 1.10-1.38 (m, 8H), 1.60-1.72 (m, 5H), 1.72-1.84 (m, 2H), 2.57 (dd, 1H), 2.70 (dd, 1H), 3.58-3.67 (m, 1H), 3.85 (s, 6H), 6.65 (s, 1H), 7.19 (s, 2H).

10 LRMS (TSP) 417 (M).

**EXAMPLE 63'**

(3*R*)-6-CYCLOHEXYL-N-HYDROXY-3-[3-(1*H*-PYRAZOL-4-YL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE

15



The title compound was obtained as a white solid from the title compound of Preparation 141', using a similar method to that described in Example 23'.

20

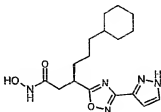
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.72-0.83 (m, 2H), 1.02-1.28 (m, 8H), 1.50-1.70 (m, 7H), 2.40-2.57 (m, 2H), 3.40-3.49 (m, 1H), 8.13 (br s, 2H), 8.78 (br s, 1H).

LRMS (TSP) 348 (M+H).

25

**EXAMPLE 64'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(1*H*-PYRAZOL-3-YL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



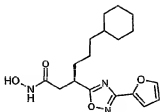
The title compound was obtained as a white solid from the title compound of Preparation 143', using a similar method to that described in Example 23'.

- 10 <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 0.73-0.94 (m, 2H), 1.00-1.38 (m, 8H), 1.54-1.82 (m, 7H), 2.57-2.79 (m, 2H), 3.56-3.69 (m, 1H), 6.64 (s, 1H), 7.47 (s, 1H), 7.65 (s, 1H).

LRMS (TSP) 348 (M+H).

15 **EXAMPLE 65'**

(3*R*)-6-CYCLOHEXYL-3-[3-(2-FURYL)-1,2,4-OXADIAZOL-5-YL]-*N*-HYDROXYHEXANAMIDE



- 20 The title compound was obtained as a colourless oil from the title compound of Preparation 145', using a similar method to that described in Example 23'.

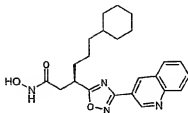
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.74-0.92 (m, 2H), 1.05-1.39 (m, 8H), 1.58-1.89 (m, 7H), 2.50-2.80 (m, 2H), 3.56-3.68 (m, 1H), 6.56 (d, 1H), 7.11 (d, 1H), 7.80 (s, 1H).

LRMS (TSP) 348 (M+H).

**EXAMPLE 66'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(3-QUINOLINYL)-1,2,4-OXADIAZOL-5-

5 YL]HEXANAMIDE



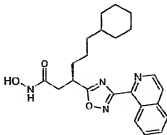
10 The title compound was obtained as a white solid from the title compound of Preparation 148', using a similar method to that described in Example 23'.

<sup>1</sup>H NMR (300 MHz, D<sub>6</sub>-DMSO) δ 0.74-0.90 (m, 2H), 1.00-1.38 (m, 8H), 1.50-1.69 (m, 5H), 1.69-1.80 (m, 2H), 2.50-2.70 (m, 2H), 3.51-3.62 (m, 1H), 7.72 (dd, 1H), 7.90 (dd, 1H), 8.11 (d, 1H), 8.22 (d, 1H), 8.80 (s, 1H), 9.00 (s, 1H), 9.42 (s, 1H), 10.53 (s, 1H).

15

**EXAMPLE 67'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(1-ISOQUINOLINYL)-1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



20

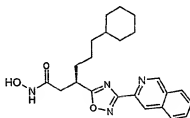
The title compound was obtained as a white solid from the title compound of Preparation 151', using a similar method to that described in Example 23'.

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O-DMSO) δ 0.74-0.92 (m, 2H), 1.00-1.40 (m, 8H), 1.50-1.69 (m, 5H), 1.69-1.82 (m, 2H), 2.52-2.70 (m, 2H), 3.57-3.66 (m, 1H), 7.76 (dd, 1H), 7.88 (dd, 1H), 8.05-8.17 (m, 2H), 8.51 (d, 1H), 8.70 (d, 1H), 8.82 (s, 1H), 10.57 (s, 1H).

5 LRMS (ES) 431 (M+Na), 409 (M+H).

#### EXAMPLE 68'

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-(3-ISOQUINOLINYL)-1,2,4-OXADIAZOL-5-  
 10 YL]HEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 154', using a similar method to that described in Example 23'.

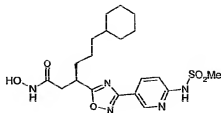
15 <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O-DMSO) δ 0.73-0.89 (m, 2H), 1.00-1.34 (m, 8H), 1.50-1.67 (m, 5H), 1.67-1.82 (m, 2H), 2.51-2.66 (m, 2H), 3.50-3.60 (m, 1H), 7.82 (dd, 1H), 7.90 (dd, 1H), 8.20 (d, 1H), 8.24 (d, 1H), 8.60 (s, 1H), 8.80 (br s, 1H), 9.46 (s, 1H), 10.55 (s, 1H).

LRMS (ES) 431 (M+Na), 409 (M+H).

20

#### EXAMPLE 69'

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[3-{6-[(METHYLSULFONYL)AMINO]-3-PYRIDINYL}-  
 1,2,4-OXADIAZOL-5-YL]HEXANAMIDE



25

The title compound was obtained as a white solid from the title compound of Preparation 156', using a similar method to that described in Example 22'. The residue was purified by trituration with diisopropyl ether.

5

Mpt 143-146 °C.

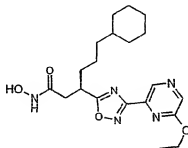
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.80-0.90 (m, 2H), 1.08-1.38 (m, 8H), 1.57-1.70 (m, 5H), 1.74-1.85 (m, 2H), 2.56 (dd, 1H), 2.68 (dd, 1H), 3.29 (s, 3H), 3.55-3.64 (m, 1H), 7.14 (d, 1H), 8.28 (d, 1H), 8.85 (s, 1H).

10

LRMS (ES) 474 (M+Na), 452 (M+H).

#### EXAMPLE 70'

15 (3*R*)-6-CYCLOHEXYL-3-[3-(6-ETHOXY-2-PYRAZINYL)-1,2,4-OXADIAZOL-5-YL]-*N*-HYDROXYHEXANAMIDE



The title compound was obtained as a white solid from the title compound of Preparation 158', using a similar method to that described in Example 23'. The reaction was performed without triethylamine and purified by preparative hplc.

20

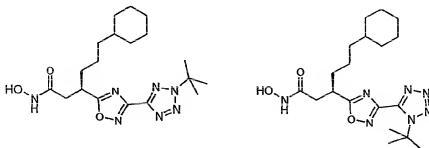
<sup>1</sup>H NMR (400MHz, D<sub>6</sub>-DMSO) δ 0.74-0.89 (m, 2H), 1.02-1.30 (m, 8H), 1.39 (t, 3H), 1.52-1.65 (m, 5H), 1.65-1.80 (m, 2H), 2.45-2.60 (m, 2H), 3.55 (m, 1H), 4.42 (q, 2H), 8.50 (s, 1H), 8.78-8.20 (m, 2H).

25

LRMS (ES) 426 (M+Na).

#### Example 71'

(3*R*)-3-[3-(2-*TERT*-BUTYL-1*H*-TETRAAZOL-5-YL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYL-*N*-HYDROXYHEXANAMIDE AND (3*R*)-3-[3-(1-*TERT*-BUTYL-2*H*-TETRAAZOL-5-YL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYL-*N*-HYDROXYHEXANAMIDE



5

To a solution of the mixture of title compounds from Preparation 160' (0.20 g, 0.52 mmol) in dried dichloromethane (3 mL) and pyridine (0.98 mL) was added 1-hydroxy-7-azabenzotriazole (0.070 g, 0.52 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.120 g, 0.62 mmol). The mixture was stirred at room temperature for 1 hour, then  
 10 hydroxylamine hydrochloride (0.108 g, 1.56 mmol) was added and then stirred at room temperature overnight. The reaction mixture was partitioned between pH 7 buffer (50 mL) and ethyl acetate (50 mL). The organic layer was separated, dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol/aqueous ammonia solution 98:2:0.2 to 95:5:0.5) to give the  
 15 title compounds, a 1:1 mixture of isomers, as a brown oil (0.085 g).

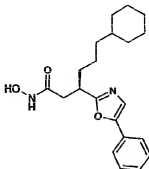
LRMS (ES) 406 (M+H).

<sup>1</sup>H NMR (400MHz, D<sub>6</sub>-DMSO) δ 0.75-0.89 (m, 4H), 1.02-1.34 (m, 18H), 1.52-1.68 (m, 22H),  
 20 1.68-1.80 (m, 8H), 2.54-2.66 (m, 2H), 2.84 (m, 2H), 3.08 (m, 2H), 3.52-3.62 (m, 2H), 8.64 (br s, 1H), 10.42 (br s, 1H).



**EXAMPLE 72'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-(5-PHENYL-1,3-OXAZOL-2-YL)HEXANAMIDE



5 The title compound was obtained as a white solid from the title compound of Preparation 164', using a similar method to that described in Example 3'. *N*-Methylmorpholine was used instead of triethylamine. Dimethylformamide was used as solvent and the residue was purified by column chromatography eluting with ethyl acetate.

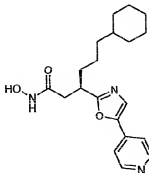
10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.75-0.96 (m, 2H), 1.00-1.40 (m, 9H), 1.50-1.90 (m, 7H), 2.44-2.60 (m, 1H), 2.64-2.80 (m, 1H), 3.40-6.0 (m, 1H), 7.16 (s, 1H), 7.24-7.44 (m, 3H), 7.50-7.62 (m, 1H), 8.30-8.57 (br s, 1H), 9.60-9.10 (br s, 1H).

LRMS (TSP) 357 (M+H).

15

**EXAMPLE 73'**

(3*R*)-6-CYCLOHEXYL-*N*-HYDROXY-3-[5-(4-PYRIDINYL)-1,3-OXAZOL-2-YL]HEXANAMIDE



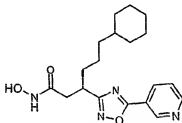
The title compound was obtained as a white solid from the title compound of Preparation 168', using a similar method to that described in Example 27'.

<sup>1</sup>H NMR (300 MHz, CH<sub>3</sub>OD) δ 0.75-0.96 (m, 2H), 1.04-1.40 (m, 9H), 1.52-1.90 (m, 8H), 2.44-2.64 (m, 2H), 3.50 (m, 1H), 7.65 (m, 3H), 8.58 (m, 2H).

LRMS (ES) 358 (M+H).

#### 10 EXAMPLE 74'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[5-(3-PYRIDINYL)-1,2,4-OXADIAZOL-3-YL]HEXANAMIDE



To a solution of the title compound from Preparation 172' (0.24 g, 0.6 mmol) in dichloromethane (10 mL) was added was added trifluoroacetic acid (5 mL) and the resulting solution was stirred at room temperature for 3 hours. The solvent and excess trifluoroacetic acid were removed *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and washed with aqueous sodium citrate solution (10 mL), brine (10 mL), then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude acid (0.2 g) was taken on to the next step without further purification.

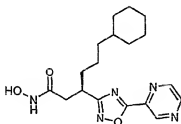
To a solution of the above crude acid (0.2 g, 0.58 mmol) in dimethylformamide (10 mL) was added N-methylmorpholine (0.064 mL, 0.18 mmol). The reaction was cooled to 0 °C in an ice bath, then *iso*-butylchloroformate (0.063 mL, 0.64 mmol) was added. Further N-methylmorpholine (0.192 mL, 1.74 mmol) was added followed by hydroxylamine hydrochloride (0.120 g, 1.74 mmol) and the reaction was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo*. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were washed with brine (25 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol 99:1:1.0 to 80:20) to give the title compound as a white foam (0.056 g).

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.77-0.92 (m, 2H), 1.04-1.40 (m, 9H), 1.58-1.88 (m, 8H), 2.46-2.68 (m, 2H), 3.50 (m, 1H), 7.64 (m, 1H), 8.54 (d, 1H), 8.80 (d, 1H), 9.28 (s, 1H).

5 LRMS (ES) 359 (M+H), 381 (M+Na),.

#### EXAMPLE 75'

(3R)-6-CYCLOHEXYL-N-HYDROXY-3-[5-(2-PYRAZINYL)-1,2,4-OXADIAZOL-3-  
10 YL]HEXANAMIDE



To a solution of the title compound from Preparation 173' (0.18 g, 0.45 mmol) in dichloromethane (8 mL) was added was added trifluoroacetic acid (4 mL) and the resulting  
15 solution was stirred at room temperature for 3 hours. The solvent and excess trifluoroacetic acid were removed *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and washed with aqueous sodium citrate solution (2 x 10 mL), brine (10 mL), then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude acid (0.17 g) was taken on to the next step without further purification.

20 To a solution of the above crude acid (0.170 g, 0.45 mmol), hydroxybenzotriazole (0.069 g, 0.45 mmol) in 1,4 - dioxane (5 mL) was added 1,3-dicyclohexylcarbodiimide (0.093 mL, 0.45 mmol). The mixture was stirred for 1.5 hours. A precipitate began to form, then 50% aqueous hydroxylamine (0.030 mL, 4.5 mmol) was added and stirring was continued overnight. The reaction mixture was filtered and the solvent removed *in vacuo*. The residue was dissolved in  
25 ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate (2 x 30 mL). The combined washings were extracted with ethyl acetate and the combined organic layers were washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue was purified by preparative hplc then triturated with ice-cold water to give the title compound as a white solid (0.064 g).

30

Mpt 126-127 °C.

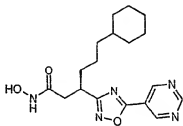
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.72-0.90 (m, 2H), 1.00-1.40 (m, 8H), 1.54-2.00 (m, 7H), 2.56-2.80 (m, 2H), 3.58 (m, 1H), 8.80 (s, 2H), 9.40 (s, 1H).

5 LRMS (ES) 382 (M+Na), 360 (M+H).

Anal. Calcd. For C<sub>18</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub> : C, 60.15; H, 7.01; N, 19.48. Found C, 60.34; H, 7.32; N, 17.12.

#### EXAMPLE 76'

10 (3R)-6-CYCLOHEXYL-N-HYDROXY-3-[5-(5-PYRIMIDINYL)-1,2,4-OXADIAZOL-3-YL]HEXANAMIDE



15 To a solution of the title compound from Preparation 174' (0.304 g, 0.76 mmol) in dichloromethane (8 mL) was added was added trifluoroacetic acid (4 mL) and the resulting solution was stirred at room temperature for 2.5 hours. The solvent and excess trifluoroacetic acid were removed *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and washed with aqueous sodium citrate solution (2 x 10 mL), brine (10 mL), then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude acid (0.276 g) was taken on to the next step without further purification.

The title compound was obtained as a white solid (0.124 g) from the above crude acid (0.276 g), using a similar method to that described in Example 3'. N-Methylmorpholine was used instead of triethylamine. The reaction mixture was acidified with 1N citric acid solution (15mL) and stirred for 4 hours. The reaction mixture was extracted with ethyl acetate (3 x 50 mL) dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was recrystallised from hexane : ethyl acetate.

25 Mpt 138-139 °C  
30

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.76-0.92 (m, 2H), 1.02-1.40 (m, 8H), 1.50-1.90 (m, 7H), 2.52-2.80 (m, 2H), 3.55 (m, 1H), 9.40 (s, 3H).

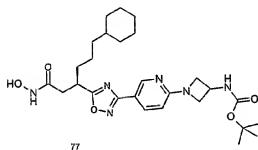
LRMS (ES) 382 (M+Na), 360 (M+H).

5

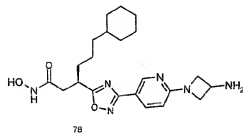
Anal. Calcd. For  $\text{C}_{18}\text{H}_{25}\text{N}_5\text{O}_3$  : C, 60.15; H, 7.01; N, 19.48. Found C, 60.15; H, 7.14; N, 19.30.

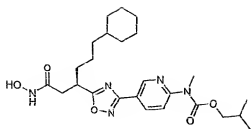
In addition to the above Examples, the following further Examples 77-81 were made using analogous methods to those mentioned above, and they exhibit PCP-inhibiting properties:

10

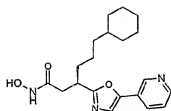


15

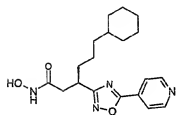




79



80



81

5

# PREPARATION 1'

10 *N*-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboximidamide



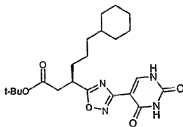
5-Cyano uracil (2.0 g, 14.6 mmol) was suspended in methanol (50 mL), then hydroxylamine hydrochloride (1.4 g, 20.0 mmol) and triethylamine (2.8 mL, 20.0 mmol) were added and the mixture was heated to reflux overnight. The mixture was cooled to room temperature, the solid was collected by filtration, washed with methanol and dried to give the title compound as a pale yellow solid (1.8 g).

<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 5.71 (br s, 2H), 7.62 s, 1H), 11.0-11.4 (br s, 1H).

LRMS (ES) 363 (2M+Na), 193 (M+Na), 171 (M+H).

## Preparation 2'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-1,2,4-oxadiazol-5-yl]hexanoate



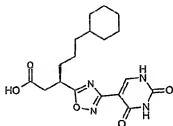
To a solution of the title compound from Preparation 175 (0.45 g, 1.5 mmol) in dichloromethane (20 mL) was added 1-hydroxybenzotriazole (0.245 g, 1.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.34 g, 1.8 mmol) followed by the title compound from Preparation 1' (0.305 g, 1.8 mmol). After 1 hour the reaction was still heterogeneous and therefore dimethylformamide (10 mL) was added to aid solubility. The reaction was stirred at room temperature overnight, then the dichloromethane was removed *in vacuo* and the remaining solution was dissolved in water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was suspended in xylene (20 mL) and then heated to reflux for 4 hours. The reaction mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (dichloromethane /methanol 95:5 as eluant) to afford the title compound as a pale yellow solid (0.60 g).

<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.73-0.95 (m, 2H), 1.03-1.20 (m, 17H), 1.52-1.73 (m, 7H), 2.64-2.74 (m, 2H), 8.00 (s, 1H), 11.0-11.7 (br s, 2H).

LRMS (ES) 887 (2M+Na), 455 (M+Na).

### Preparation 3'

(3*R*)-6-Cyclohexyl-3-[3-(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



To a solution of the title compound from Preparation 2' (0.58 g, 1.34 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (10 mL) and the resulting green solution was stirred at room temperature for 2 hours. The solvent and excess trifluoroacetic acid were removed *in vacuo*, the residue was azeotroped with toluene to give a brown solid which was triturated with diisopropyl ether. The solid was collected by filtration and dried under high vacuum to give the title compound as a white solid (0.40 g).

Mpt 240-244 °C.

<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO) δ 0.72-0.89 (m, 2H), 1.03-1.17 (m, 8H), 1.53-1.72 (m, 7H), 2.66-2.81 (m, 2H), 3.36-3.47 (m, 1H), 8.01 (s, 1H), 11.32 (br s, 1H), 11.38 (br s, 1H), 12.05-12.30 (br s, 1H).

LRMS (ES) 375 (M-H).

### PREPARATION 4'

N'-HYDROXY-6-METHYL-3-PYRIDAZINECARBOXIMIDAMIDE





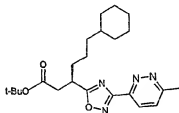
3-Cyano-6-methyl pyridazine (US 5914319) (0.77 g, 6.4 mmol) was dissolved in methanol (20 mL), then hydroxylamine hydrochloride (0.66 g, 9.6 mmol) and triethylamine (1.3 mL, 9.6 mmol) were added and the mixture was stirred at room temperature overnight. The mixture was chilled in an ice-bath, then the solid was collected by filtration, washed with methanol and dried to give the title compound as a pale yellow solid (0.84 g).

<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO) δ 2.48 (s, 3H), 5.76 (s, 2H), 8.47 (s, 1H), 8.90 (s, 1H), 9.95 (s, 1H).

LRMS (ES) 153 (M+H).

#### Preparation 5'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(6-methyl-3-pyridazinyl)-1,2,4-oxadiazol-5-yl]hexanoate



To a solution of the title compound from Preparation 175 (0.45 g, 1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added 1-hydroxybenzotriazole (0.245 g, 1.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.34 g, 1.8 mmol) followed by the title compound from Preparation 4' (0.28 g, 1.8 mmol). After 1 hour the reaction was still heterogeneous and therefore dimethylformamide (5 mL) was added to aid solubility. The reaction was stirred at room temperature overnight, then the dichloromethane was removed *in vacuo* and the remaining solution was dissolved in water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was dissolved in xylene (15 mL) and then heated to reflux for overnight. The reaction mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was

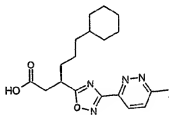
purified by flash chromatography on silica gel (dichloromethane /methanol 99:1 as eluant) to afford the title compound as a viscous yellow oil (0.40 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.75-0.88 (m, 2H), 1.07-1.22 (m, 6H), 1.23-1.34 (m, 2H), 1.37 (s, 9H), 1.58-1.70 (m, 5H), 1.71-1.92 (m, 2H), 2.66 (s, 3H), 2.72 (dd, 1H), 2.93 (dd, 1H), 3.54-3.62 (m, 1H), 8.62 (s, 1H), 9.22 (s, 1H).

LRMS (ES) 851 (2M+Na), 437 (M+Na).

#### Preparation 6'

(3*R*)-6-Cyclohexyl-3-[3-(6-methyl-3-pyridazinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



To a solution of the title compound from Preparation 5' (0.38 g, 0.92 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL) and the resulting solution was stirred at room temperature for 1 hour. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene to give the title compound as a yellow oil (0.33 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.75-0.88 (m, 2H), 1.03-1.38 (m, 6H), 1.58-1.70 (m, 5H), 1.71-1.92 (m, 2H), 2.69 (s, 3H), 2.87 (dd, 1H), 3.09 (dd, 1H), 2.54-2.62 (m, 1H), 8.68 (s, 1H), 9.24 (s, 1H).

LRMS (ES) 357 (M-H).

#### PREPARATION 7'

*N*-HYDROXY-1-METHYL-1*H*-IMIDAZOLE-2-CARBOXIMIDAMIDE

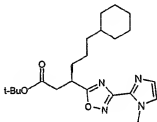


1-Methyl-2-cyanoimidazole (0.85 g, 8.0 mmol) (J. Chem. Soc. Perkin Trans. I 1994, 239) was dissolved in methanol (20 mL), then hydroxylamine hydrochloride (0.66 g, 9.6 mmol) and triethylamine (1.3 mL, 9.6 mmol) were added and the mixture was stirred at room temperature for 1 hour. The mixture was chilled in an ice-bath, then the solid was collected by filtration, washed with methanol and dried to give the title compound as a white crystalline solid which was contaminated with triethylamine hydrochloride (0.90 g).

<sup>1</sup>H NMR (400MHz, D<sub>6</sub>-DMSO) δ 3.78 (s, 3H), 5.52 (br s, 2H), 6.88 (s, 1H), 7.14 (s, 1H), 9.68 (s, 1H).

#### Preparation 8'

*tert*-Butyl (3*R*)-6-cyclohexyl-*N*-hydroxy-3-[3-(1-methyl-1*H*-imidazol-2-yl)-1,2,4-oxadiazol-5-yl]hexanoate



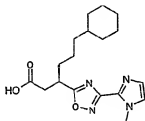
To a solution of the title compound from Preparation 175 (0.60 g, 2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added 1-hydroxybenzotriazole (0.32 g, 2.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.45 g, 2.4 mmol) followed by the title compound from Preparation 7' (0.40 g, 2.2 mmol) and triethylamine (0.32 mL, 2.4 mmol). The reaction was stirred at room temperature overnight, then the solution was diluted with dichloromethane (30 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was dissolved in xylene (10 mL) and then heated to reflux for 48 hours. The reaction mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 2:1 as eluant) to afford the title compound as a viscous yellow oil (0.62 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.92 (m, 2H), 1.08-1.34 (m, 8H), 1.39 (s, 9H), 1.56-1.92 (m, 7H), 2.66 (dd, 1H), 2.91 (dd, 1H), 3.48-3.56 (m, 1H), 4.00 (s, 3H), 7.01 (s, 1H), 7.20 (s, 1H).

LRMS (ES) 827 (2M+Na), 425 (M+Na).

#### Preparation 9'

- 5 (3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(1-methyl-1*H*-imidazol-2-yl)-1,2,4-oxadiazol-5-yl]hexanoic acid



- 10 To a solution of the title compound from Preparation 8' (0.59 g, 1.5 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL) and the resulting solution was stirred at room temperature for 1 hour. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene to give the title compound as a yellow gum (0.52 g).
- 15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.92 (m, 2H), 1.06-1.26 (m, 6H), 1.27-1.40 (m, 2H), 1.56-1.95 (m, 7H), 2.81 (dd, 1H), 2.97 (dd, 1H), 3.51-3.60 (m, 1H), 4.15 (s, 3H), 7.25 (s, 1H), 7.54 (s, 1H).

LRMS (ES) 345 (M-H).

#### 20 PREPARATION 10'

*N*-HYDROXY-6-METHYL-2-OXO-1,2-DIHYDRO-3-PYRIDINECARBOXIMIDAMIDE



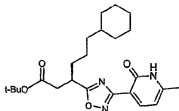
- 25 The title compound was obtained as a pale yellow solid from 2-hydroxy-3-cyano-6-methylpyridine, using a similar method to that described in Preparation 1'.

<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO) δ 2.19 (s, 3H), 6.07 (d, 1H), 6.19 (s, 2H), 7.81 (d, 1H).

LRMS (ES) 190 (M+Na), 168 (M+H).

#### Preparation 11'

- 5 *tert*-Butyl (3*R*)-6-cyclohexyl-*N*-hydroxy-3-[3-(6-methyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoate



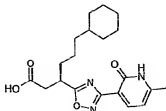
- 10 The title compound was obtained as a white foam from the title compound from Preparation 175 and the title compound from Preparation 10', using a similar method to that described in Preparation 2'.

- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.90 (m, 2H), 1.13-1.21 (m, 6H), 1.23-1.34 (m, 2H), 1.39 (s, 9H), 1.63-1.82 (m, 7H), 2.44 (s, 3H), 2.63 (dd, 1H), 2.82 (dd, 1H), 3.47-3.54 (m, 1H), 6.20 (d, 1H), 8.25 (d, 1H).

LRMS (ES) 881 (2M+Na), 452 (M+Na).

#### 20 Preparation 12'

(3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(6-methyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



- 25 The title compound was obtained as a white solid from the title compound from Preparation 11', using a similar method to that described in Preparation 3'.

Mpt 189-192 °C

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.90 (m, 2H), 1.11-1.27 (m, 6H), 1.27-1.41 (m, 2H), 1.56-1.87 (m, 7H), 2.33 (s, 3H), 2.79 (dd, 1H), 2.97 (dd, 1H), 3.51-3.60 (m, 1H), 6.19 (d, 1H), 8.23 (d, 1H).

LRMS (ES) 372 (M-H).

#### PREPARATION 13'

##### 6-Oxo-1,6-dihydro-3-pyridazinecarboxitrile



6-Oxo-1,6-dihydropyridazine-3-carboxamide (J. Chem. Soc. 1948, 2195) (1.1 g, 8.0 mmol) was suspended in dichloromethane (20 mL), cooled to 0 °C then pyridine (1.3 mL, 16 mmol) and trifluoroacetic anhydride (1.2 mL, 8.4 mmol) were added and the reaction was stirred at room temperature for 1 hour. A further 5 mL of pyridine was added to aid solubility and then the reaction was warmed to room temperature and stirred overnight. The mixture was diluted with water (100 mL) and then extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed *in vacuo*, with residual pyridine removed by azeotroping with toluene. The residue was purified by flash chromatography on silica gel (dichloromethane /methanol 95:5 as eluant) to give the title compound as an off-white solid (0.8 g).

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.03 (d, 1H), 7.40 (d, 1H), 11.23 (br s, 1H).

#### PREPARATION 14'

##### N-Hydroxy-6-oxo-1,6-dihydro-3-pyridazinecarboximidamide



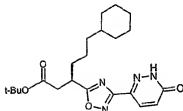
The title compound was obtained as a pale yellow solid from the title compound from Preparation 13', using a method similar to that described in Preparation 4'.

<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO) δ 5.52 (s, 2H), 6.82 (d, 1H), 7.70 (d, 1H), 10.04 (s, 1H), 12.95 (br s, 1H).

LRMS (ES) 177 (M+Na), 155 (M+H).

#### Preparation 15'

*tert*-Butyl (3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(6-oxo-1,6-dihydro-3-pyridazinyl)-1,2,4-oxadiazol-5-yl]hexanoate



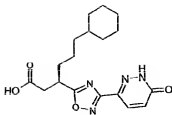
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the title compound from Preparation 14', using a method similar to that described in Preparation 2'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.92 (m, 2H), 1.12-1.57 (m, 17H), 1.58-1.92 (m, 7H), 2.69 (dd, 1H), 2.88 (dd, 1H), 3.50-3.57 (m, 1H), 7.04 (d, 1H), 7.94 (s, 1H).

LRMS (ES) 855 (2M+Na), 439 (M+Na), 417 (M+H).

#### Preparation 16'

(3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(6-oxo-1,6-dihydro-3-pyridazinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was isolated as a white solid from the title compound from Preparation 15', using a method similar to that described in Preparation 3'.

Mpt 170-172 °C

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.93 (m, 2H), 1.12-1.40 (m, 8H), 1.58-1.73 (m, 5H), 1.73-1.91 (m, 2H), 2.84 (dd, 1H), 3.09 (dd, 1H), 3.56-3.67 (m, 1H), 7.06 (d, 1H), 7.96 (d, 1H).

LRMS (ES) 359 (M-H).

#### PREPARATION 17'

##### N'-HYDROXY-2-PYRIMIDINECARBOXIMIDAMIDE



The title compound was obtained as a pale yellow solid from 2-cyanopyrimidine, using a similar method to that described in Preparation 7'.

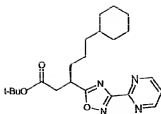
<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O) δ 5.71 (s, 2H), 7.46 (d, 1H), 8.80 (d, 2H), 10.03 (s, 1H).

LRMS (ES) 161 (M+Na), 139 (M+H).

#### Preparation 18'

*tert*-Butyl (3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(2-pyrimidinyl)-1,2,4-oxadiazol-5-yl]hexanoate





The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the title compound from Preparation 17', using a similar method to that described in Preparation 5'.

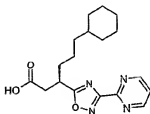
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.76-0.91 (m, 2H), 1.05-1.44 (m, 17H), 1.55-1.69 (m, 5H), 1.70-1.81 (m, 1H), 1.81-1.97 (m, 1H), 2.70 (dd, 1H), 2.94 (dd, 1H), 3.55-3.63 (m, 1H), 7.40 (dd, 1H), 8.93 (d, 2H).

LRMS (ES) 823 (2M+Na), 423 (M+Na), 401 (M+H).

Anal. Calcd. For C<sub>22</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub> + 0.2 CH<sub>2</sub>Cl<sub>2</sub>: C, 63.87; H, 7.82; N, 13.42. Found C, 64.02; H, 7.89; N, 13.30.

#### Preparation 19'

(3R)-6-Cyclohexyl-N-hydroxy-3-[3-(2-pyrimidinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



To a solution of the title compound from Preparation 18' (0.78 g, 1.95 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2 mL) and the resulting solution was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene give the title compound as a yellow oil (0.67 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.76-0.92 (m, 2H), 1.07-1.26 (m, 6H), 1.26-1.40 (m, 2H), 1.55-1.69 (m, 5H), 1.72-1.96 (m, 2H), 2.86 (dd, 1H), 3.13 (dd, 1H), 3.60-3.69 (m, 1H), 7.43 (dd, 1H), 8.97 (d, 2H).

5 LRMS (ES) 343 (M-H).

#### PREPARATION 20'

##### N'-HYDROXY-5-PYRIMIDINECARBOXIMIDAMIDE



10

5-Cyanopyrimidine (J. Org. Chem. 1962, 27, 2264) (0.64 g, 6.1 mmol) was dissolved in methanol (20 mL), the solution was cooled to 0 °C then hydroxylamine hydrochloride (0.42 g, 6.1 mmol) and triethylamine (0.84 mL, 6.1 mmol) were added and the mixture was heated to reflux overnight. The mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The residue was pre-absorbed onto silica gel, and purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia – 95:5:0.5 as eluant) to give a yellow solid which was contaminated with triethylamine hydrochloride. Recrystallisation from ethanol gave the title compound as a white solid (0.44 g).

20

Mpt 172-175 °C

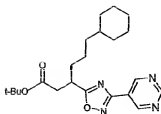
<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO) δ 6.01 (s, 2H), 8.99 (s, 2H), 9.14 (s, 1H), 9.95 (s, 1H).

25 Anal. Calcd. For C<sub>5</sub>H<sub>6</sub>N<sub>4</sub>O: C, 43.48; H, 4.38; N, 40.56. Found C, 43.46; H, 4.36; N, 40.27.

#### Preparation 21'

*tert*-Butyl (3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(5-pyrimidinyl)-1,2,4-oxadiazol-5-yl]hexanoate

30



The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the title compound from Preparation 20', using a similar method to that described in Preparation 5'.

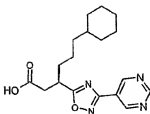
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.91 (m, 2H), 1.10-1.46 (m, 8H), 1.39 (s, 9H), 1.58-1.88 (m, 7H), 2.70 (dd, 1H), 2.96 (dd, 1H), 3.50-3.60 (m, 1H), 9.32 (s, 1H), 9.37 (s, 2H).

LRMS (ES) 423 (M+Na), 401 (M+H).

Anal. Calcd. For C<sub>22</sub>H<sub>32</sub>N<sub>4</sub>O<sub>5</sub>: C, 65.97; H, 8.05; N, 13.99. Found C, 65.93; H, 8.11; N, 13.65.

#### Preparation 22'

(3R)-6-Cyclohexyl-N-hydroxy-3-[(5-pyrimidinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was obtained as a yellow oil from the title compound of Preparation 21', using a similar method to that described in Preparation 19'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.93 (m, 2H), 1.12-1.28 (m, 6H), 1.28-1.40 (m, 2H), 1.58-1.73 (m, 5H), 1.74-1.91 (m, 2H), 2.83 (dd, 1H), 3.04 (dd, 1H), 3.56-3.63 (m, 1H), 9.35 (s, 1H), 9.40 (s, 2H).

LRMS (ES) 343 (M-H).

**PREPARATION 23'****3-Methoxy-5-isoxazolecarbonitrile**

5

3-Methoxy-5-isoxazolecarboxamide (J. Chem Soc. 1968, 172) (1.0 g, 7.0 mmol) was dissolved in dichloromethane (20 mL), cooled to 0 °C then pyridine (1.1 mL, 14 mmol) and trifluoroacetic anhydride (1.0 mL, 7.4 mmol) were added and the reaction was stirred at 0 °C for 40 minutes. The mixture was diluted with dichloromethane (10 mL) and then washed with 5% aqueous citric acid solution (3 x 20 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed *in vacuo* to give the title compound as a yellow oil (0.69 g).

10

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 4.04 (s, 3H), 6.51 (s, 1H).

15 **PREPARATION 24'****N-HYDROXY-3-METHOXY-5-ISOXAZOLECARBOXIMIDAMIDE**

20 The title compound was obtained as a white solid from the title compound from Preparation 23', using a similar method to that described in Preparation 20'.

Mpt 173-174 °C

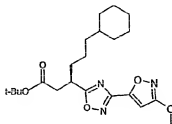
25 <sup>1</sup>H NMR (400MHz, D<sub>2</sub>O) δ 3.89 (s, 3H), 5.86 (s, 2H), 6.43 (s, 1H), 10.06 (s, 1H).

Anal. Calcd. For C<sub>5</sub>H<sub>7</sub>N<sub>3</sub>O<sub>5</sub>: C, 38.22; H, 4.49; N, 26.74. Found C, 38.25; H, 4.43; N, 26.41.

**Preparation 25'**

30

*tert*-Butyl (3*R*)-6-cyclohexyl-*N*-hydroxy-3-[3-(3-methoxy-5-isoxazolyl)-1,2,4-oxadiazol-5-yl]hexanoate



5

The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the title compound from Preparation 24', using a similar method to that described in Preparation 5'.

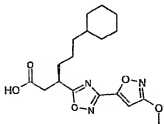
10 <sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 0.73-0.86 (m, 2H), 1.04-1.28 (m, 8H), 1.29 (s, 9H), 1.50-1.65 (m, 5H), 1.65-1.76 (m, 2H), 2.76 (m, 2H), 3.44-3.63 (m, 1H), 3.97 (s, 3H), 7.02 (s, 1H).

LRMS (ES) 861 (2M+Na), 442 (M+Na).

15 Anal. Calcd. For C<sub>22</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub> + 0.5 PhMe + 0.1 CH<sub>2</sub>Cl<sub>2</sub>: C, 64.86; H, 7.91; N, 8.86. Found C, 64.73; H, 7.94; N, 8.63.

#### Preparation 26'

20 (3*R*)-6-cyclohexyl-*N*-hydroxy-3-[3-(3-methoxy-5-isoxazolyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



25 The title compound was obtained as a yellow oil from the title compound of Preparation 25', using a similar method to that described in Preparation 19'.

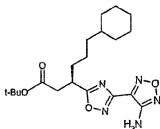
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.79-0.90 (m, 2H), 1.11-1.34 (m, 8H), 1.58-1.72 (m, 5H), 1.72-1.86 (m, 2H), 2.80 (dd, 1H), 3.01 (dd, 1H), 3.52-3.61 (m, 1H), 4.04 (s, 3H), 6.55 (s, 1H).

LRMS (ES) 362 (M-H).

Anal. Calcd. For  $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_5$ : C, 59.49; H, 6.93; N, 11.56. Found C, 59.08; H, 7.00; N, 11.32.

#### Preparation 27'

*tert*-Butyl (3*R*)-3-[3-(4-Amino-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl-*N*-hydroxyhexanoate



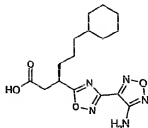
To a solution of the title compound from Preparation 175 (0.50 g, 1.7 mmol) in dichloromethane (20 mL) was added 1-hydroxybenzotriazole (0.23 g, 1.7 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.35 g, 1.85 mmol), *N*-methylmorpholine (0.20 mL, 1.85 mmol) and 4-amino-*N*-hydroxy-1,2,5-oxadiazole-3-carboximidamide (0.24 g, 1.7 mmol) and the reaction was stirred at room temperature for 48 hours. Water (20 mL) was added, stirring was continued for 20 minutes and then the layers were separated using a Whatman 5 micron cartridge. The organic layer was concentrated *in vacuo*, the residue was then dissolved in xylene (15 mL) and heated to reflux for 24 hours. The reaction was cooled and the solution was purified by flash chromatography on silica gel (graded elution of ethyl acetate/pentane 0:100 to 20:80) to give the title compound as a brown oil (0.13 g).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.79-0.93 (m, 2H), 1.11-1.37 (m, 8H), 1.40 (s, 9H), 1.58-1.91 (m, 7H), 2.71 (dd, 1H), 2.90 (dd, 1H), 3.54-3.62 (m, 1H), 5.00 (s, 2H).

LRMS (ES) 428 (M+Na), 405 (M+H).

#### Preparation 28'

(3*R*)-3-[3-(4-Amino-1,2,5-oxadiazol-3-yl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl-*N*-hydroxyhexanoic acid



5

To the title compound of Preparation 27' (0.21 g, 0.5 mmol) was added hydrogen chloride in dioxane (3 mL of 4M solution) and the reaction was stirred at room temperature for 72 hours. The solvent was removed *in vacuo* and a further portion of hydrogen chloride in dioxane was added (3 mL of 4M solution) and stirring was continued at room temperature for 6 hours. The solvent was then removed *in vacuo* and the residue was dried under high vacuum to give the title compound as a yellow oil (0.19 g).

10

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 0.75-0.87 (m, 2H), 1.02-1.31 (m, 8H), 1.51-1.66 (m, 5H), 1.66-1.89 (m, 2H), 2.79 (dd, 1H), 2.87 (dd, 1H), 3.45-3.56 (m, 1H), 6.37 (s, 2H).

15

LRMS (ES) 348 (M-H).

#### PREPARATION 29'

ETHYL 5-[AMINO(HYDROXYIMINO)METHYL]NICOTINATE

20



Ethyl-(5-cyano-3-pyridyl)carboxylate (WO 96/30372) (1.8 g, 10.2 mmol) was dissolved in methanol (50 mL), the solution was cooled to 0 °C then hydroxylamine hydrochloride (0.71 g, 10.2 mmol) and triethylamine (1.4 mL, 10.2 mmol) were added and the mixture was stirred at room temperature for 72 hours. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol 95:5

25

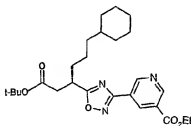
to 93:7) to give the title compound as a white solid which contained 0.3 equivalents of triethylamine hydrochloride (2.5 g).

$^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.40 (t, 3H), 4.42 (q, 2H), 8.59 (s, 1H), 9.00 (s, 1H), 9.10 (s, 1H).

LRMS (ES) 210 (M+H).

#### Preparation 30'

Ethyl 5-[5-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl]nicotinate



To a solution of the title compound from Preparation 175 (3.05 g, 10.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added 1,1-carbonyldiimidazole (1.66 g, 10.2 mmol), and the reaction was stirred at room temperature overnight. The title compound from Preparation 29' (2.52 g, 10.2 mmol) was added and the mixture was stirred at room temperature for 72 hours. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (100 mL) and washed with water (3 x 100 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated. The pale yellow residue was dissolved in xylene (200 mL) and the reaction was heated to reflux for 48 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (graded elution with ethyl acetate/pentane 20:80 to 25:75) to give the title compound as a colourless oil (3.14 g).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.79-0.92 (m, 2H), 1.09-1.48 (m, 20H), 1.58-1.71 (m, 5H), 1.71-1.90 (m, 2H), 2.69 (dd, 1H), 2.87 (dd, 1H), 3.50-3.59 (m, 1H), 4.45 (q, 2H) 8.92 (s, 1H), 9.34 (s, 1H), 9.42 (s, 1H).

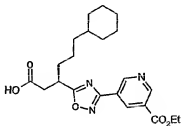
LRMS (ES) 494 (M+Na), 472 (M+H).

Anal. Calcd. For  $\text{C}_{26}\text{H}_{37}\text{N}_3\text{O}_5$ : C, 66.22; H, 7.91; N, 8.91. Found C, 66.17; H, 7.90; N, 8.74.



**Preparation 31'**

(3*R*)-6-Cyclohexyl-3-[3-[5-(ethoxycarbonyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



5

The title compound of Preparation 30' (0.70 g, 1.5 mmol) was dissolved in trifluoroacetic acid (5 mL) and the reaction was stirred at room temperature for 1.5 hours. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene and then dichloromethane to give the title compound as a colourless oil (0.73 g).

10

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.91 (m, 2H), 1.08-1.40 (m, 8H), 1.43 (t, 3H), 1.57-1.72 (m, 5H), 1.72-1.94 (m, 2H), 2.83 (dd, 1H), 3.07 (dd, 1H), 3.56-3.64 (m, 1H), 4.47 (q, 2H) 9.09 (s, 1H), 9.33 (s, 1H), 9.45 (s, 1H), 10.80 (br s, 1H).

15

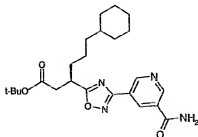
LRMS (ES) 438 (M+Na), 416 (M+H).

Anal. Calcd. For C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub> + 1.2 TFA: C, 53.06; H, 5.51; N, 7.61. Found C, 53.00; H, 5.61; N, 7.59.

20

**Preparation 32'**

*tert*-Butyl (3*R*)-3-[3-[5-(aminocarbonyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoate



25

To a solution of the title compound from Preparation 30' (0.62 g, 1.3 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was added concentrated aqueous ammonia solution (1.5 mL) and the reaction was sealed then heated to 50 °C overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (graded elution with ethyl acetate/hexane 50:50 to 75:25) to give the title compound as a colourless oil (0.12 g).

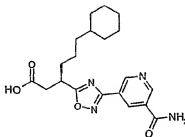
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.90 (m, 2H), 1.08-1.44 (m, 17H), 1.57-1.71 (m, 5H), 1.71-1.89 (m, 2H), 2.68 (dd, 1H), 2.87 (dd, 1H), 3.50-3.58 (m, 1H), 6.00 (br s, 2H), 8.85 (s, 1H), 9.36 (s, 1H), 9.42 (s, 1H).

LRMS (ES) 465 (M+Na), 443 (M+H).

Anal. Calcd. For C<sub>28</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>: C, 65.14; H, 7.74; N, 12.66. Found C, 65.14; H, 7.77; N, 12.61.

#### 15 Preparation 33'

(3*R*)-3-{3-[5-(Aminocarbonyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoic acid



The title compound was obtained as a white foam from the title compound of Preparation 32', using a similar method to that described in Preparation 31'.

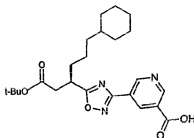
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.91 (m, 2H), 1.08-1.40 (m, 8H), 1.56-1.72 (m, 5H), 1.72-1.92 (m, 2H), 2.83 (dd, 1H), 3.01 (dd, 1H), 3.53-3.62 (m, 1H), 6.74 (br s, 2H), 8.84 (s, 1H), 9.16 (s, 1H), 9.35 (s, 1H).

LRMS (ES) 385 (M-H).

Anal. Calcd. For C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> + 0.8 TFA: C, 54.31; H, 5.66; N, 11.73. Found C, 54.29; H, 5.85; N, 11.50.

**Preparation 34'**

5-[*(1R)*-1-(2-*tert*-Butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl]nicotinic acid



To a solution of the title compound from Preparation 30' (1.0 g, 2.1 mmol) in tetrahydrofuran (7 mL) was added lithium hydroxide (0.18 g, .2 mmol) and the reaction was stirred vigorously at room temperature for 1.5 hours. The mixture was diluted with water (10 mL), acidified to pH1 with 2M aqueous hydrochloric acid and then extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was removed *in vacuo* to give the title compound as a colourless oil which solidified on standing (0.95 g).

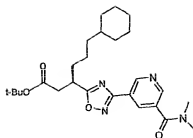
<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.80-0.92 (m, 2H), 1.08-1.44 (m, 17H), 1.57-1.73 (m, 5H), 1.73-1.91 (m, 2H), 2.71 (dd, 1H), 2.90 (dd, 1H), 3.52-3.60 (m, 1H), 9.00(s, 1H), 9.39 (s, 1H), 9.51 (s, 1H).

LRMS (ES) 442 (M-H).

Anal. Calcd. For  $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_5$ : C, 64.99; H, 7.50; N, 9.47. Found C, 65.00; H, 7.48; N, 9.38.

**Preparation 35'**

*tert*-Butyl (3*R*)-6-cyclohexyl-3-(5-[(dimethylamino)carbonyl]-3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoate



To a solution of the title compound from Preparation 34' (0.48 g, 1.1 mmol) in tetrahydrofuran (7 mL) was added 1,1-carbonyldiimidazole (0.19 g, 1.2 mmol) and the reaction was stirred at room temperature for 15 hours. Dimethylamine (1.9 mL of 5.6M solution in ethanol, 10.7 mmol) was added and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (graded elution with ethyl acetate/pentane 50:50 to 75:25) to give the title compound as a viscous oil (0.43 g).

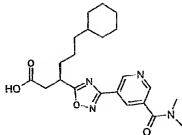
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.87 (m, 2H), 1.08-1.42 (m, 17H), 1.57-1.83 (m, 7H), 2.68 (dd, 1H), 2.87 (dd, 1H), 3.04 (s, 3H), 3.15 (s, 3H), 3.48-3.56 (m, 1H), 8.41 (s, 1H), 8.78 (s, 1H), 9.32 (s, 1H).

LRMS (ES) 493 (M+Na), 471 (M+H).

Anal. Calcd. For C<sub>28</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> + 0.15 EtOAc: C, 65.94; H, 8.16; N, 11.70. Found C, 65.96; H, 8.12; N, 11.66.

#### Preparation 36'

(3R)-6-Cyclohexyl-3-(3-{5-[(dimethylamino)carbonyl]-3-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



The title compound was obtained as a white foam from the title compound of Preparation 35', using a similar method to that described in Preparation 31'.

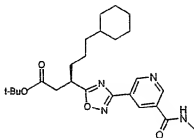
- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.88 (m, 2H), 1.06-1.35 (m, 8H), 1.60-1.70 (m, 5H), 1.70-1.86 (m, 2H), 2.83 (dd, 1H), 3.05 (dd, 1H), 3.07 (s, 3H), 3.18 (s, 3H), 3.53-3.61 (m, 1H), 8.65 (s, 1H), 8.87 (s, 1H), 9.36 (s, 1H).

LRMS (ES) 413 (M-H).

- Anal. Calcd. For C<sub>22</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> + 1.35 TFA: C, 52.19; H, 5.56; N, 9.86. Found C, 52.28; H, 5.68; N, 9.72.

#### Preparation 37'

- tert-Butyl (3R)-6-cyclohexyl-3-{3-[(methylamino)carbonyl]-3-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoate



- The title compound was obtained as a viscous oil from the title compound from Preparation 34' and methylamine in THF (2M solution), using a similar method to that described in Preparation 35'.

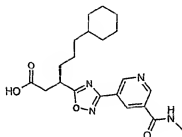
- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.85 (m, 2H), 1.04-1.41 (m, 17H), 1.58-1.84 (m, 7H), 2.69 (dd, 1H), 2.88 (dd, 1H), 3.05 (s, 3H), 3.48-3.56 (m, 1H), 6.36 (br s, 1H), 8.67 (s, 1H), 9.11 (s, 1H), 9.38 (s, 1H).

LRMS (ES) 479 (M+Na), 457 (M+H).

- Anal. Calcd. For C<sub>25</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> + 0.25 EtOAc: C, 65.25; H, 8.00; N, 11.71. Found C, 65.11; H, 8.02; N, 11.79.

**Preparation 38'**

(3*R*)-6-Cyclohexyl-3-(3-[5-[(methylamino)carbonyl]-3-pyridinyl]-1,2,4-oxadiazol-5-yl)hexanoic acid



The title compound was obtained as a sticky gum from the title compound of Preparation 37', using a similar method to that described in Preparation 31'.

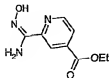
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.88 (m, 2H), 1.09-1.35 (m, 8H), 1.58-1.70 (m, 5H), 1.70-1.84 (m, 2H), 2.84 (dd, 1H), 3.02 (dd, 1H), 3.08 (d, 3H), 3.50-3.60 (m, 1H), 9.00 (s, 1H), 9.23 (s, 1H), 9.31 (s, 1H).

LRMS (ES) 399 (M-H).

Anal. Calcd. For C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> + 1.4 TFA + 0.4 PhMe: C, 53.52; H, 5.5650 N, 9.39. Found C, 53.65; H, 5.66; N, 9.74.

**Preparation 39'**

Ethyl 2-[amino(hydroxylimino)methyl]isonicotinate



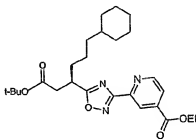
The title compound was obtained as a pale yellow solid from ethyl-2-cyanoisonicotinate (Heterocycles 1987, 26, 731) using a similar method to that described in Preparation 4'.

<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O-DMSO) δ 1.28 (t, 3H), 4.34 (q, 2H), 5.87 (s, 2H), 7.78 (d, 1H), 8.25 (s, 1H), 8.70 (d, 1H), 10.03 (s, 1H).

5 LRMS (ES) 210 (M+H).

#### Preparation 40'

10 Ethyl 2-[5-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl]isonicotinate



The title compound was obtained as a colourless oil from the title compound from Preparation 175 and the amidoxime from Preparation 39; using a similar method to that described in Preparation 30'.

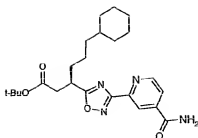
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.92 (m, 2H), 1.08-1.48 (m, 20H), 1.57-1.71 (m, 5H), 1.71-1.94 (m, 2H), 2.69 (dd, 1H), 2.92 (dd, 1H), 3.53-3.61 (m, 1H), 4.46 (q, 2H) 7.95 (d, 1H), 8.64 (s, 1H), 9.82 (d, 1H).

20 LRMS (ES) 494 (M+Na), 472 (M+H).

Anal. Calcd. For C<sub>28</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub> + 0.2 EtOAc: C, 65.80; H, 7.95; N, 8.59. Found C, 65.81; H, 7.89; N, 8.68.

#### Preparation 41'

25 *tert*-Butyl (3*R*)-3-[3-[4-(aminocarbonyl)-2-pyridinyl]-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoate



To a solution of the title compound from Preparation 40' (0.60 g, 1.3 mmol) in ethanol (3 mL) was added a saturated solution of ammonia in ethanol (15 mL) and the reaction was stirred at room temperature for 1.5 hours. Ammonia gas was bubbled through the reaction mixture for 30 minutes and then the reaction was stirred at room temperature for 48 hours. More ammonia gas was bubbled through the reaction mixture and the reaction was stirred at room temperature for 24 hours. The reaction mixture at this stage contained predominantly starting material. Concentrated aqueous ammonia solution (1 mL) was added, the reaction system was sealed and stirred at room temperature for 72 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (graded elution with ethyl acetate/hexane 50:50 to 75:25) to give the title compound as a colourless oil (0.10 g).

<sup>1</sup>H NMR (400 MHz, <sup>2</sup>CDCl<sub>3</sub>) δ 0.79-0.92 (m, 2H), 1.10-1.50 (m, 17H), 1.57-1.70 (m, 5H), 1.70-1.92 (m, 2H), 2.71 (dd, 1H), 2.92 (dd, 1H), 3.51-3.60 (m, 1H), 7.80 (d, 1H), 8.39 (s, 1H), 8.92 (d, 1H).

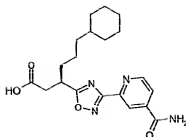
LRMS (ES) 465 (M+Na).

Anal. Calcd. For C<sub>24</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> + 0.15 EtOAc: C, 64.83; H, 7.78; N, 12.29. Found C, 64.68; H, 7.83; N, 12.44.

#### Preparation 42'

(3R)-3-[4-{(Aminocarbonyl)-2-pyridinyl}-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid





The title compound was obtained as a white solid from the title compound of Preparation 41', using a similar method to that described in Preparation 31'.

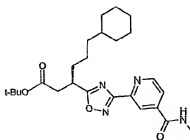
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 0.79-0.91 (m, 2H), 1.08-1.40 (m, 8H), 1.58-1.70 (m, 5H), 1.76-1.86 (m, 2H), 2.82 (dd, 1H), 2.97 (dd, 1H), 3.55-3.62 (m, 1H), 7.91 (d, 1H), 8.53 (s, 1H), 8.82 (d, 1H).

LRMS (ES) 385 (M-H).

Anal. Calcd. For C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub> + 0.1 TFA: C, 60.98; H, 6.61; N, 14.08. Found C, 60.94; H, 6.67; N, 14.09.

### Preparation 43'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-((3-((4-((methylamino)carbonyl)-2-pyridinyl)-1,2,4-oxadiazol-5-yl)hexanoate



To a solution of the title compound from Preparation 40' (0.50 g, 1.1 mmol) in ethanol (10 mL) was added methylamine (2.7 mL of 2M in tetrahydrofuran, 5.4 mmol)) and the reaction was stirred at room temperature for 72 hours. The reaction was then heated to 45 °C for 24 hours.

The solvent was removed *in vacuo* and the residue was purified by flash chromatography on

silica gel (graded elution with ethyl acetate/hexane 50:50 to 75:25) to give the title compound as a colourless oil (0.18 g).

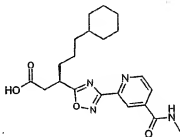
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.92 (m, 2H), 1.12-1.46 (m, 17H), 1.58-1.71 (m, 5H), 1.71-1.92 (m, 2H), 2.70 (dd, 1H), 2.91 (dd, 1H), 3.07 (d, 3H), 3.52-3.60 (m, 1H), 6.23 (br s, 1H), 7.78 (d, 1H), 8.34 (s, 1H), 8.90 (d, 1H).

LRMS (ES) 479 (M+Na), 457 (M+H).

- 10 Anal. Calcd. For C<sub>26</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub> + 0.15 EtOAc: C, 65.45; H, 7.98; N, 11.93. Found C, 65.24; H, 8.01; N, 12.13.

#### Preparation 44'

- 15 (3*R*)-6-Cyclohexyl-3-(3-{4-[(methylamino)carbonyl]-2-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



- 20 The title compound was obtained as a colourless gum from the title compound of Preparation 43', using a similar method to that described in Preparation 31'.

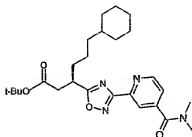
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.09-1.38 (m, 8H), 1.55-1.70 (m, 5H), 1.70-1.91 (m, 2H), 2.84 (dd, 1H), 3.00-3.11 (m, 4H), 3.53-3.63 (m, 1H), 6.64 (br s, 1H), 7.82 (s, 1H), 8.35 (s, 1H), 8.88 (d, 1H).

LRMS (ES) 399 (M-H).

Anal. Calcd. For C<sub>21</sub>H<sub>29</sub>N<sub>4</sub>O<sub>4</sub> + 0.95 TFA + 0.1 H<sub>2</sub>O: C, 53.87; H, 5.75; N, 10.97. Found C, 54.18; H, 5.83; N, 10.58.

## Preparation 45'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-(3-{4-[(dimethylamino)carbonyl]-2-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoate



To a solution of the title compound from Preparation 40' (0.50 g, 1.1 mmol) in tetrahydrofuran (4 mL) was added dimethylamine (2.0 mL of 5.6M in ethanol, 10.6 mmol). The reaction flask was sealed and the reaction was stirred at 60 °C for 48 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (graded elution with ethyl acetate/hexane 50:50 to 75:25 to 100% ethyl acetate) to give the title compound as a colourless oil (0.14 g).

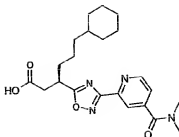
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.08-1.40 (m, 17H), 1.48-1.92 (m, 7H), 2.68 (dd, 1H), 2.89 (dd, 1H), 2.95 (s, 3H), 3.12 (s, 3H), 3.52-3.60 (m, 1H), 7.38 (s, 1H), 8.10 (s, 1H), 8.84 (s, 1H).

LRMS (ES) 493 (M+Na), 471 (M+H).

Anal. Calcd. For C<sub>28</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> + 0.15 H<sub>2</sub>O: C, 65.98; H, 8.16; N, 11.84. Found C, 65.89; H, 8.14; N, 11.75.

## Preparation 46'

(3*R*)-6-Cyclohexyl-3-(3-{4-[(dimethylamino)carbonyl]-2-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



The title compound was obtained as a pale yellow oil from the title compound of Preparation 45', using a similar method to that described in Preparation 31'.

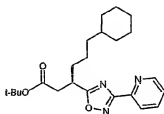
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.09-1.38 (m, 8H), 1.56-1.72 (m, 5H), 1.72-1.91 (m, 2H), 2.82 (dd, 1H), 2.94-3.17 (m, 7H), 3.55-3.64 (m, 1H), 7.45 (s, 1H), 8.14 (s, 1H), 8.87 (d, 1H).

LRMS (ES) 413 (M-H).

Anal. Calcd. For C<sub>22</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> + 1.0 TFA: C, 54.54; H, 5.91; N, 10.60. Found C, 54.62; H, 6.23; N, 10.45.

#### Preparation 47'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoate



To a solution of the title compound from Preparation 175 (0.30 g, 1.0 mmol) in dichloromethane (15 mL) was added 1,1-carbonyldiimidazole (0.16 g, 1.0 mmol). The reaction was stirred at room temperature for 2 hours then *N*-hydroxy-2-pyridinecarboximidamide (0.14 g, 1.0 mmol) was added and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was heated at 120 °C for 2 hours. The residue was then purified by flash chromatography on silica gel (dichloromethane /methanol/aqueous ammonia solution 99:1:0.1 as eluant) to give the title compound as a colourless oil (0.25 g).

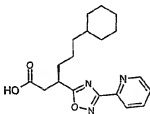
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.07-1.40 (m, 17H), 1.60-1.70 (m, 5H), 1.70-1.94 (m, 2H), 2.70 (dd, 1H), 2.94 (dd, 1H), 3.50-3.60 (m, 1H), 7.38-7.44 (m, 1H), 7.80-7.86 (m, 1H), 8.14 (d, 1H), 8.80 (d, 1H).

5

LRMS (ES) 422 (M+Na), 400 (M+H).

#### Preparation 48'

10 (3*R*)-6-Cyclohexyl-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was obtained as a pale brown oil from the title compound of Preparation 45', using a similar method to that described in Preparation 31'.

15

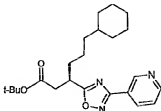
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.76-0.93 (m, 2H), 1.06-1.37 (m, 8H), 1.56-1.71 (m, 5H), 1.71-1.94 (m, 2H), 2.93 (dd, 1H), 3.12 (dd, 1H), 3.55-3.65 (m, 1H), 7.46-7.55 (m, 1H), 7.90-7.96 (m, 1H), 8.18 (d, 1H), 8.83 (d, 1H).

20

LRMS (TSP) 366 (M+Na), 344 (M+H).

#### Preparation 49'

25 *tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoate



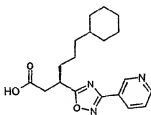
To a solution of the title compound from Preparation 175 (1.0 g, 3.3 mmol) in dichloromethane (30 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.65 g, 3.3 mmol), 4-dimethylamino pyridine (0.07 g, 0.6 mmol), and *N*-hydroxy-3-pyridinecarboximidamide (0.45 g, 1.0 mmol) and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was heated at 120 °C for 8 hours. The residue was then purified by flash chromatography on silica gel (dichloromethane /methanol 95:5 as eluant) to give the title compound as a colourless oil (1.07 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.93 (m, 2H), 1.08-1.44 (m, 17H), 1.57-1.88 (m, 7H), 2.70 (dd, 1H), 2.87 (dd, 1H), 3.48-3.59 (m, 1H), 7.41 (dd, 1H), 8.30-8.38 (m, 1H), 8.69-8.75 (m, 1H), 9.30 (s, 1H).

LRMS (TSP) 422 (M+Na), 400 (M+H).

#### 15 Preparation 50'

(3*R*)-6-Cyclohexyl-3-[3-(3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



20

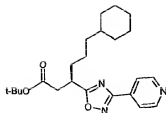
The title compound was obtained as an off-white solid from the title compound of Preparation 49', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79-0.93 (m, 2H), 1.06-1.40 (m, 8H), 1.59-1.74 (m, 5H), 1.74-1.89 (m, 2H), 2.84 (dd, 1H), 3.07 (dd, 1H), 3.55-3.65 (m, 1H), 7.79 (dd, 1H), 8.75 (d, 1H), 8.91 (d, 1H), 9.40 (s, 1H).

LRMS (TSP) 366 (M+Na), 344 (M+H).

#### 30 Preparation 51'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoate



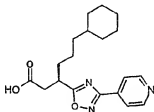
The title compound was obtained as a colourless oil from the title compound of Preparation 175 and *N*-hydroxy-4-pyridinecarboximidamide, using a similar method to that described in Preparation 47'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.08-1.41 (m, 17H), 1.56-1.87 (m, 7H), 2.70 (dd, 1H), 2.87 (dd, 1H), 3.50-3.58 (m, 1H), 7.94 (d, 2H), 8.79 (d, 2H).

LRMS (TSP) 422 (M+Na), 400 (M+H).

#### Preparation 52'

(3*R*)-6-Cyclohexyl-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was obtained as a white solid from the title compound of Preparation 51', using a similar method to that described in Preparation 68'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.93 (m, 2H), 1.06-1.40 (m, 8H), 1.60-1.75 (m, 5H), 1.75-1.90 (m, 2H), 2.87 (dd, 1H), 3.06 (dd, 1H), 3.55-3.65 (m, 1H), 8.30 (d, 2H), 8.91 (d, 2H).

LRMS (TSP) 366 (M+Na), 344 (M+H).

#### Preparation 53'

*N*'-Hydroxy-6-methyl-3-pyridinecarboximidamide

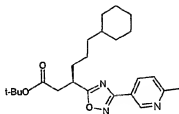


- 5 The title compound was obtained as a white solid from 2-methyl-4-cyanopyridine, using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  2.55 (s, 3H), 4.85 (s, 2H), 7.32 (d, 1H), 7.95 (d, 1H), 8.66 (s, 1H).

10 **Preparation 54'**

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(6-methyl-3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoate



15

The title compound was obtained as a colourless oil from the title compound of Preparation 175 and the amidoxime from Preparation 53', using a similar method to that described in Preparation 47'.

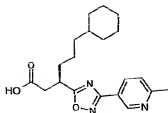
- 20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.75-0.90 (m, 2H), 1.03-1.41 (m, 17H), 1.58-1.84 (m, 7H), 2.61 (s, 3H), 2.67 (dd, 1H), 2.88 (dd, 1H), 3.47-3.57 (m, 1H), 7.23 (s, 1H), 8.21 (d, 1H), 9.17 (s, 1H).

LRMS (ES) 436 (M+Na), 414 (M+H).

25 **Preparation 55'**

(3*R*)-6-Cyclohexyl-3-[3-(6-methyl-3-pyridinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid





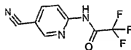
The title compound was obtained as a colourless oil from the title compound of Preparation 55', using a similar method to that described in Preparation 31'. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol 98:2 to 95:5).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.92 (m, 2H), 1.08-1.39 (m, 8H), 1.59-1.74 (m, 5H), 1.74-1.90 (m, 2H), 2.70 (s, 3H), 2.81 (dd, 1H), 3.05 (dd, 1H), 3.52-3.82 (m, 1H), 7.42 (d, 1H), 8.43 (s, 1H), 9.21 (s, 1H).

LRMS (ES) 358 (M+H).

#### Preparation 56'

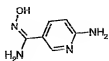
*N*-(5-Cyano-2-pyridinyl)-2,2,2-trifluoroacetamide



To a solution of 6-aminonicotinonitrile (2.0 g, 15 mmol) and pyridine (4.7 mL, 58 mmol) in tetrahydrofuran (80 mL) at 0 °C was added trifluoroacetic anhydride (4.5 mL, 32 mmol) slowly, ensuring internal temperature did not exceed 5 °C. Once addition was complete the reaction was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo*, the residue was then dissolved in ethyl acetate (100 mL) and washed with water (50 mL) then dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane 1:1 as eluant) to give the title compound as a white solid (2.7 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02 (d, 1H), 8.30 (d, 1H), 8.53-8.75 (m, 2H).

#### Preparation 57'

6-Amino-*N*<sup>3</sup>-hydroxy-3-pyridinecarboximidamide

- 5 The title compound was obtained as a white solid from the title compound of Preparation 56', using a similar method to that described in Preparation 4'.

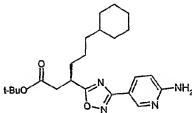
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 6.55 (d, 1H), 7.67 (dd, 1H), 8.18 (d, 1H).

- 10 LRMS (ES) 153 (M+H).

**Preparation 58'**

*tert*-Butyl (3*R*)-3-[3-(6-amino-3-pyridinyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl hexanoate

- 15



The title compound was obtained as a yellow oil from the title compound of Preparation 175 and the amidoxime from Preparation 57', using a similar method to that described in Preparation 47'.

- 20

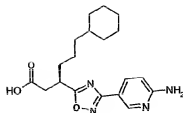
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.91 (m, 2H), 1.10-1.45 (m, 17H), 1.55-1.87 (m, 7H), 2.64 (dd, 1H), 2.83 (dd, 1H), 3.45-3.52 (m, 1H), 4.71 (s, 2H), 6.52 (d, 1H), 8.07 (d, 1H), 8.86 (s, 1H).

LRMS (ES) 415 (M+H).

- 25

**Preparation 59'**

(3*R*)-3-[3-(6-Amino-3-pyridinyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



The title compound from Preparation 58' was dissolved in trifluoroacetic acid (5 mL) and the reaction was stirred at room temperature for 2 hours. The solution was evaporated to dryness and then the residue was azeotroped with toluene. The residue was dissolved in ethyl acetate (20 mL) and extracted with saturated sodium bicarbonate solution (20 mL). The organic layer was discarded and the aqueous layer was acidified to pH5 with 10% citric acid solution and then extracted with ethyl acetate (2 x 50mL). The combined organic extracts were washed with 10% citric acid solution (20 mL), water (20 mL) and then dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* to give the title compound as a white solid (0.22 g).

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 0.81-0.90 (m, 2H), 1.10-1.38 (m, 8H), 1.59-1.72 (m, 5H), 1.72-1.81 (m, 2H), 2.77 (dd, 1H), 2.90 (dd, 1H), 3.46-3.56 (m, 1H), 4.50 (br s, 2H), 6.64 (d, 1H), 8.00 (d, 1H), 8.55 (s, 1H).

LRMS (ES) 359 (M+H).

#### Preparation 60'

2-(Dimethylamino)-N'-hydroxy-4-pyridinecarboximidamide



To a solution of hydroxylamine hydrochloride (0.47 g, 7.0 mmol) in methanol (10 mL) was added sodium metal (0.16 g, 7.0 mmol) portionwise. After all the sodium metal had dissolved 4-cyano-2-dimethylaminopyridine (1.0 g, 7.0 mmol) was added and the reaction was heated to reflux for 4 hours. The reaction was cooled to room temperature, filtered to remove precipitated sodium chloride and the filtrate was evaporated to dryness. The residue was dissolved in ethanol in order to crystallise the product but this was unsuccessful, so the solvent was removed *in vacuo* to give the title compound as a white solid (1.7 g), which was contaminated with ethanol.

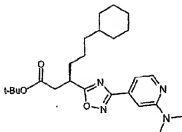
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.10 (s, 6H), 4.50-5.00 (br s, 3H), 6.65-6.73 (m, 2H), 8.16 (s, 1H).

LRMS (ES) 181 (M+H).

5

#### Preparation 61'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-{3-[2-(dimethylamino)-4-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoate



10

To a solution of the title compound from Preparation 175 (1.0 g, 3.3 mmol) in dichloromethane (30 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.65 g, 3.3 mmol), 4-dimethylamino pyridine (0.04 g, 0.3 mmol), and the amidoxime from Preparation 60' (0.61 g, 3.3 mmol). Dimethylformamide (1 mL) was added to aid solubility and the reaction was stirred at room temperature overnight. The solution was washed with water (2 x 25 mL), saturated sodium bicarbonate solution (25 mL) and brine (30 mL). The organic layer was dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was heated at 120 °C for 2 hours. The residue was cooled to room temperature and then purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 98:2:0.2 as eluant) to give the title compound as a brown oil (0.50 g).

15

20

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.72-0.86 (m, 2H), 1.00-1.43 (m, 17H), 1.52-1.88 (m, 7H), 2.65 (dd, 1H), 2.83 (dd, 1H), 3.12 (s, 6H), 3.43-3.55 (m, 1H), 7.10-7.14 (m, 2H), 8.22 (d, 1H).

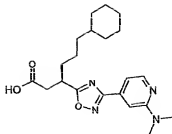
25

LRMS (TSP) 443 (M+H).

#### Preparation 62'

30

(3*R*)-6-Cyclohexyl-3-{3-[2-(dimethylamino)-4-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



The title compound was obtained as a colourless oil from the title compound of Preparation 61', using a similar method to that described in Preparation 31'.

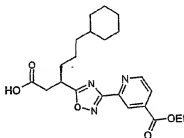
5

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.86 (m, 2H), 1.02-1.46 (m, 8H), 1.53-1.91 (m, 7H), 2.82 (dd, 1H), 3.01 (dd, 1H), 3.38 (s, 6H), 3.50-3.60 (m, 1H), 7.47 (d, 1H), 7.58 (s, 1H), 8.10 (d, 1H).

#### Preparation 63'

10

(3*R*)-6-Cyclohexyl-3-[(3-{4-(ethoxycarbonyl)-2-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoyl]hexanoic acid



15 The title compound was obtained as a pale yellow oil from the title compound of Preparation 40', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.74-0.87 (m, 2H), 1.04-1.38 (m, 8H), 1.41 (t, 3H), 1.55-1.70 (m, 5H), 1.70-1.91 (m, 2H), 2.83 (dd, 1H), 3.06 (dd, 1H), 3.53-3.62 (m, 1H), 4.43 (q, 2H), 8.04 (d, 1H), 8.67 (s, 1H), 8.90 (d, 1H).

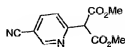
20

LRMS (TSP) 416 (M+H).

#### Preparation 64'

25

Dimethyl 2-(5-cyano-2-pyridinyl)malonate



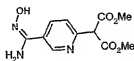
Dimethylmalonate (1.4 mL, 11.9 mmol) was added to a suspension of sodium hydride (0.48 g of a 60% dispersion in mineral oil, 11.9 mmol) in dimethylformamide (50 mL) at 0 °C. The reaction was stirred at 0°C for 1.5 hours, then 2-chloro-5-cyanopyridine (1.5 g, 10.8 mmol) was added and the reaction was stirred at room temperature for 1 hour and then heated to 100°C for 3 hours. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (diethyl ether as eluant) to give the title compound as a colourless oil (1.1 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.78 (s, 6H), 5.02 (s, 1H), 7.67 (d, 1H), 7.98(dd, 1H), 8.82 (d, 1H).

LRMS (ES)491 (2M+Na), 257 (M+Na), 235 (M+H).

#### Preparation 65'

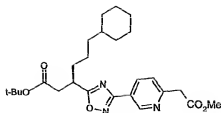
Diethyl 2-(5-[amino(hydroxyimino)methyl]-2-pyridinyl)malonate



The title compound was obtained crude as a pale yellow solid from the title compound of Preparation 64', using a similar method to that described in Preparation 31'. The title compound was used in the next reaction without purification or characterisation.

#### Preparation 66'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-[6-(2-methoxy-2-oxoethyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoate



The title compound was obtained as a brown oil from the title compound of Preparation 175 and the amidoxime from Preparation 65', using a similar method to that described in Preparation 47'.

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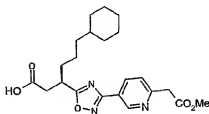
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.92 (m, 2H), 1.02-1.47 (m, 17H), 1.54-1.90 (m, 7H), 2.68 (dd, 1H), 2.87 (dd, 1H), 3.49-3.58 (m, 1H), 3.74 (s, 3H), 3.93 (s, 2H), 7.42 (d, 1H), 8.32 (d, 1H), 9.23 (s, 1H).

10 LRMS (ES) 494 (M+Na), 472 (M+H).

**Preparation 67'**

(3R)-6-Cyclohexyl-3-{3-[6-(2-methoxy-2-oxoethyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid

15



The title compound was obtained as a pale yellow oil from the title compound of Preparation 66', using a similar method to that described in Preparation 31'.

20

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.90 (m, 2H), 1.02-1.40 (m, 8H), 1.54-1.71 (m, 5H), 1.71-1.91 (m, 2H), 2.80 (dd, 1H), 3.03 (dd, 1H), 3.52-3.62 (m, 1H), 3.71 (s, 3H), 3.93 (s, 2H), 7.42 (d, 1H), 8.33 (d, 1H), 9.21 (s, 1H).

25 LRMS (TSP) 415 (M).

**Preparation 68'**

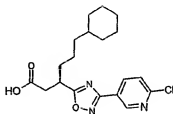




LRMS (TSP) 433 (M).

#### Preparation 70'

- 5 (3R)-3-[3-(6-Chloro-3-pyridinyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



The title compound of Preparation 69' (3.0 g, 6.9 mmol) was dissolved in trifluoroacetic acid (10 mL) and the reaction was stirred at room temperature for 3 hours. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene and then dichloromethane. The residue was dissolved in ethyl acetate (100 mL) and then washed with saturated aqueous sodium dihydrogen citrate solution (100 mL) and water (100 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo* to give the title compound as a yellow oil (2.7 g).

15

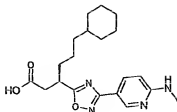
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.92 (m, 2H), 1.06-1.42 (m, 8H), 1.56-1.89 (m, 7H), 2.82 (dd, 1H), 3.05 (dd, 1H), 3.51-3.61 (m, 1H), 7.46 (d, 1H), 8.31 (dd, 1H), 9.08 (d, 1H).

LRMS (TSP) 378 (M+H).

20

#### Preparation 71'

(3R)-6-Cyclohexyl-3-[3-[6-(methylamino)-3-pyridinyl]-1,2,4-oxadiazol-5-yl] hexanoic acid



25

The title compound from Preparation 70' (0.8 g, 2.1 mmol) and methylamine (2.0 mL of a 33% solution in ethanol, 21 mmol) were heated in a sealed reaction vessel at 90 °C for 10 hours. The

reaction mixture was cooled to room temperature and the residue was purified by flash chromatography on silica gel (graded elution of ethyl acetate/hexane 50:50 to ethyl acetate/acetic acid 99:1) to give the title compound as a colourless oil (0.24 g).

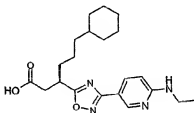
- 5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.90 (m, 2H), 1.02-1.41 (m, 8H), 1.53-1.70 (m, 5H), 1.70-1.86 (m, 2H), 2.75 (dd, 1H), 2.89 (s, 3H), 2.97 (dd, 1H), 3.51-3.61 (m, 1H), 6.48 (d, 1H), 8.14 (dd, 1H), 8.58 (d, 1H).

LRMS (TSP) 373 (M+H).

10

#### Preparation 72'

(3*R*)-6-Cyclohexyl-3-[3-[6-(ethylamino)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



15

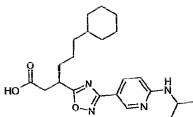
The title compound was obtained as a colourless oil from the title compound of Preparation 70' and ethylamine, using a similar method to that described in Preparation 71'.

- 20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.84-0.92 (m, 2H), 1.06-1.45 (m, 11H), 1.53-1.88 (m, 7H), 2.76 (dd, 1H), 2.98 (dd, 1H), 3.15 (q, 2H), 3.55-3.63 (m, 1H), 6.48 (d, 1H), 8.12 (dd, 1H), 8.58 (d, 1H).

LRMS (TSP) 387 (M+H, 100%).

- 25 **Preparation 73'**

(3*R*)-6-Cyclohexyl-3-[3-[6-(isopropylamino)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



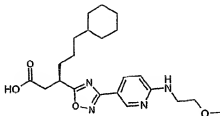
The title compound was obtained as a colourless oil (0.04 g) from the title compound of Preparation 70' (0.27g) and isopropylamine, using a similar method to that described in Preparation 71' apart from copper sulphate (0.27 g, 1.1 mmol) was added to speed up the reaction.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.79-0.92 (m, 2H), 1.10-1.40 (m, 14H), 1.58-1.81 (m, 7H), 2.79 (dd, 1H), 2.92 (dd, 1H), 3.56-3.65 (m, 1H), 4.02-4.11 (m, 1H), 6.65 (d, 1H), 7.98 (dd, 1H), 8.57 (d, 1H).

LRMS (TSP) 401 (M+H).

#### Preparation 74'

(3R)-6-Cyclohexyl-3-(3-[6-[(2-methoxyethyl)amino]-3-pyridinyl]-1,2,4-oxadiazol-5-yl)hexanoic acid



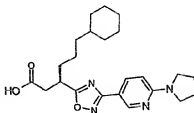
The title compound was obtained as a colourless oil from the title compound of Preparation 70' and 2-methoxyethylamine, using a similar method to that described in Preparation 71'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.08-1.42 (m, 8H), 1.57-1.70 (m, 5H), 1.70-1.91 (m, 2H), 2.79 (dd, 1H), 3.02 (dd, 1H), 3.37 (s, 3H), 3.50 (t, 2H), 3.56-3.65 (m, 1H), 3.58 (t, 2H), 6.52 (d, 1H), 8.07 (dd, 1H), 8.68 (d, 1H).

LRMS (TSP) 415 (M-H).

**Preparation 75'**

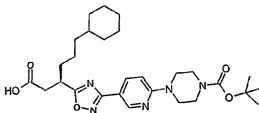
- 5 (3*R*)-6-Cyclohexyl-3-{3-[6-(1-pyrrolidinyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl} hexanoic acid



- 10 The title compound was obtained as a colourless oil from the title compound of Preparation 70' and pyrrolidine, using a similar method to that described in Preparation 71'.

**Preparation 76'**

- 15 (3*R*)-3-(3-{6-[4-(*tert*-Butoxycarbonyl)-1-piperaziny]-3-pyridinyl}-1,2,4-oxadiazol-5-yl)-6-cyclohexylhexanoic acid



- 20 The title compound was obtained as a viscous oil from the title compound of Preparation 70' and BOC-piperazine, using a similar method to that described in Preparation 71'.

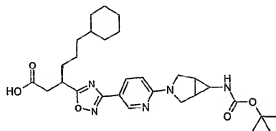
- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.92 (m, 2H), 1.03-1.39 (m, 8H), 1.47 (s, 9H), 1.55-1.70 (m, 5H), 1.70-1.89 (m, 2H), 2.77 (dd, 1H), 2.99 (dd, 1H), 3.48-3.55 (m, 9H), 6.62 (d, 1H), 8.08 (d, 1H), 8.81(s, 1H).

25

LRMS (ES) 528 (M+H).

**Preparation 77'**

(3*R*)-3-[3-(6-[(*tert*-Butoxycarbonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



5

The title compound was obtained as a viscous oil from the title compound of Preparation 70' and *tert*-butyl 3-azabicyclo[3.1.0]hex-6-ylcarbamate (J. Chem. Soc. Perkin Trans. I 2000, 1615), using a similar method to that described in Preparation 71'.

10

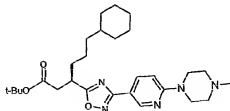
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.90 (m, 2H), 1.07-1.52 (m, 17H), 1.52-1.90 (m, 9H), 2.77 (dd, 1H), 2.98 (dd, 1H), 3.40-3.60 (m, 3H), 3.60-3.81 (m, 2H), 4.80-5.40 (br, 1H), 7.31 (d, 1H), 8.02 (d, 1H), 8.20-8.80 (br s, 1H), 8.78 (s, 1H).

15 LRMS (TSP) 540 (M+H).

#### Preparation 78'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-[6-(4-methyl-1-piperazinyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoate

20



A mixture of the title compound from Preparation 69' (0.4 g, 0.9 mmol) and *N*-methylpiperazine (4.1 mL, 37 mmol) were heated in a sealed reaction vessel at 90 °C for 1.5 hours. The reaction was cooled to room temperature, the residue was dissolved in ethyl acetate (50 mL) and washed with 10% aqueous citric acid solution (30 mL) followed by saturated aqueous sodium

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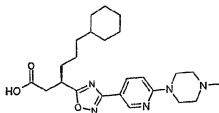
bicarbonate solution (30 mL). The organic layer was dried ( $\text{MgSO}_4$ ) and the solvent was removed *in vacuo* to give the title compound as a viscous oil (0.41 g).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.76-0.90 (m, 2H), 1.04-1.40 (m, 17H), 1.58-1.84 (m, 7H), 2.35 (s, 3H), 2.47-2.55 (m, 4H), 2.67 (dd, 1H), 2.86 (dd, 1H), 3.44-3.54 (m, 1H), 3.65-3.72 (m, 4H), 6.68 (d, 1H), 8.08 (dd, 1H), 8.86 (d, 1H).

LRMS (ES) 498 ( $\text{M}+\text{H}$ ).

#### 10 Preparation 79'

(3R)-6-Cyclohexyl-3-{3-[6-(4-methyl-1-piperazinyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



15

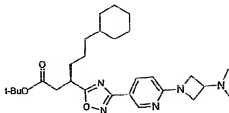
The title compound of Preparation 78' (0.41 g, 0.8 mmol) was dissolved in trifluoroacetic acid (5 mL) and the reaction was stirred at room temperature for 2.5 hours. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene and then dichloromethane. The residue was dissolved in ethyl acetate (50 mL) and then washed with saturated aqueous sodium bicarbonate solution (30 mL). The organic layer was dried ( $\text{MgSO}_4$ ) and the solvent was removed *in vacuo* to give the title compound as a yellow oil (0.26 g).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.76-0.90 (m, 2H), 1.00-1.40 (m, 8H), 1.56-1.86 (m, 7H), 2.42 (s, 3H), 2.54-2.80 (m, 5H), 2.90 (dd, 1H), 3.41-3.58 (m, 5H), 6.20 (d, 1H), 7.87 (dd, 1H), 8.66 (d, 1H).

LRMS (ES) 442 ( $\text{M}+\text{H}$ ).

#### 30 Preparation 80'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-(3-{6-[3-(dimethylamino)-1-azetidinyl]-3-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoate



5

To a solution of 3-dimethylamino azetidine bis-trifluoroacetic acid salt (0.76 g, 2.3 mmol) in ethanol (5 mL) was added triethylamine (0.64 mL, 4.6 mmol) and the mixture was stirred at room temperature for 20 minutes. The title compound from Preparation 69' (0.5 g, 1.15 mmol) was added and the mixture was heated in a sealed reaction vessel at 100 °C for 48 hours. The reaction was cooled to room temperature, then purified by flash chromatography on silica gel (ethyl acetate/hexane/diethylamine 70:30:1 as eluant) to give the title compound as a viscous oil (0.41 g).

10

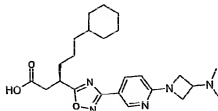
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.73-0.90 (m, 2H), 1.07-1.42 (m, 17H), 1.57-1.88 (m, 7H), 2.22 (s, 6H), 2.66 (dd, 1H), 2.85 (dd, 1H), 3.21-3.30 (m, 1H), 3.42-3.52 (m, 1H), 3.83-3.97 (m, 2H), 4.09-4.18 (m, 2H), 6.32 (d, 1H), 8.05 (dd, 1H), 8.81 (d, 1H).

15

LRMS (ES) 498 (M+H).

## 20 Preparation 81'

(3*R*)-6-Cyclohexyl-3-(3-{6-[3-(dimethylamino)-1-azetidinyl]-3-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



25

The title compound was obtained as a white solid from the title compound of Preparation 80', using a similar method to that described in Preparation 79'.

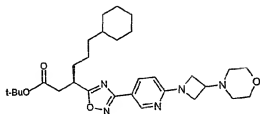
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.91 (m, 2H), 1.06-1.41 (m, 8H), 1.55-1.86 (m, 7H), 2.26 (s, 6H), 2.68 (dd, 1H), 2.87 (dd, 1H), 3.32-3.40 (m, 1H), 3.43-3.52 (m, 1H), 3.94-4.00 (m, 2H), 4.07-4.14 (m, 2H), 6.25 (d, 1H), 8.02 (dd, 1H), 8.78 (d, 1H).

5

LRMS (ES) 442 (M+H).

#### Preparation 82'

- 10 *tert*-Butyl (3*R*)-6-cyclohexyl-3-{3-[6-[3-(4-morpholinyl)-1-azetidinyl]-3-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoate



- 15 The title compound was obtained as a viscous oil from the title compound of Preparation 69' and 3-*N*-morpholinoazetidine, using a similar method to that described in Preparation 78'.

- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.73-0.88 (m, 2H), 1.00-1.45 (m, 17H), 1.53-1.88 (m, 7H), 2.38-2.48 (m, 4H), 2.63 (dd, 1H), 2.82 (dd, 1H), 3.49-3.60 (m, 1H), 3.60-3.71 (m, 1H), 3.66-3.77 (m, 4H), 3.92-3.99 (m, 2H), 4.05-4.18 (m, 2H), 6.32 (d, 1H), 8.04 (dd, 1H), 8.80 (d, 1H).

20

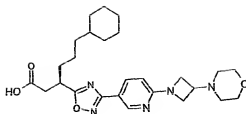
LRMS (TSP) 540 (M+H).

#### Preparation 83'

25

(3*R*)-6-Cyclohexyl-3-{3-[6-[3-(4-morpholinyl)-1-azetidinyl]-3-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid





The title compound was obtained as a white solid from the title compound of Preparation 82', using a similar method to that described in Preparation 79'.

5

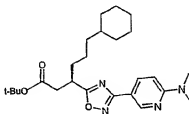
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.91 (m, 2H), 1.02-1.40 (m, 8H), 1.53-1.87 (m, 7H), 2.42-2.52 (m, 4H), 2.72 (dd, 1H), 2.94 (dd, 1H), 3.30-3.40 (m, 1H), 3.44-3.55 (m, 1H), 3.71-3.79 (m, 4H), 3.96-4.03 (m, 2H), 4.08-4.19 (m, 2H), 6.30 (d, 1H), 8.06 (dd, 1H), 8.79 (d, 1H).

10 LRMS (TSP) 483 (M).

#### Preparation 84'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-[6-(dimethylamino)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoate

15



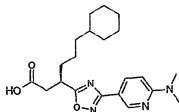
To a solution of the title compound from Preparation 69' (0.41 g, 0.9 mmol) in ethanol (10 mL) was added dimethylamine (1.7 mL of 5.6M solution in ethanol, 9.3 mmol) and the reaction was heated to 70 °C for 9 hours. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (hexane/diethyl ether 1:1 as eluant) to give the title compound as a clear oil (0.42 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.89 (m, 2H), 1.08-1.22 (m, 6H), 1.28-1.40 (m, 11H), 1.56-1.87 (m, 7H), 2.66 (dd, 1H), 2.85 (dd, 1H), 3.15 (s, 6H), 3.45-3.63 (m, 1H), 6.53 (d, 1H), 8.06 (dd, 1H), 8.84 (d, 1H).

25 LRMS (TSP) 443 (M+H).

**Preparation 85'**

(3*R*)-5-Cyclohexyl-3-{3-[6-(dimethylamino)-3-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



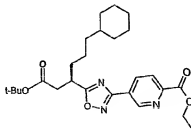
The title compound was obtained as a yellow oil from the title compound of Preparation 84', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.75-0.90 (m, 2H), 1.06-1.38 (m, 8H), 1.56-1.83 (m, 7H), 2.78 (dd, 1H), 2.99 (dd, 1H), 3.38 (s, 6H), 3.45-3.55 (m, 1H), 6.92 (d, 1H), 8.30 (dd, 1H), 8.74 (d, 1H).

LRMS (TSP) 387 (M+H).

**Preparation 86'**

Ethyl 5-[5-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl]-2-pyridinecarboxylate



To a solution of the title compound from Preparation 69' (0.5 g, 1.15 mmol) in ethanol (6.5 mL) was added triethylamine (0.64 mL, 4.6 mmol), palladium(II) acetate (0.03 g, 10 mol%) and triphenylphosphine (0.06 g, 20 mol%) and the reaction was heated under 100psi of carbon monoxide at 50 °C for 24 hours. Further catalyst (10 mol% of palladium(II) acetate and 20 mol% of triphenylphosphine) was added and the carbonylation was continued at 50 °C/100psi for

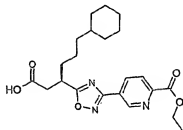
a further 72 hours. The reaction was cooled to room temperature, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane 10:90 as eluant) to give the title compound as a colourless oil (0.24 g).

- 5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.93 (m, 2H), 1.02-1.51 (m, 20H), 1.55-1.94 (m, 7H), 2.70 (dd, 1H), 2.89 (dd, 1H), 3.50-3.60 (m, 1H), 4.52 (q, 2H), 8.25 (d, 1H), 8.50 (dd, 1H), 9.42 (d, 1H).

LRMS (TSP) 472 (M+H).

# 10 Preparation 87'

(3R)-6-Cyclohexyl-3-{3-[6-(ethoxycarbonyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



15

The title compound was obtained as a colourless oil from the title compound of Preparation 86', using a similar method to that described in Preparation 31'.

- 20 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-0.92 (m, 2H), 1.00-1.39 (m, 8H), 1.46 (t, 3H), 1.55-1.72 (m, 5H), 1.72-1.91 (m, 2H), 2.83 (dd, 1H), 3.06 (dd, 1H), 3.55-3.64 (m, 1H), 4.50 (q, 2H), 8.25 (d, 1H), 8.52 (dd, 1H), 9.42 (d, 1H).

LRMS (ES) 438 (M+Na), 416 (M+H).

# 25 Preparation 88'

2-Chloro-N'-hydroxy-3-pyridinecarboximidamide



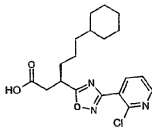
Sodium methoxide (150 mL of 0.25M solution in methanol, 37.5 mmol) was added to a solution of hydroxylamine hydrochloride (2.8 g, 39.7 mmol) in methanol (150 mL), and the reaction was stirred at room temperature for 30 minutes. The mixture was filtered, then 2-chloro-3-cyanopyridine (5.0 g, 36.1 mmol) was added, the reaction was stirred at room temperature for 16 hours and then heated to reflux for 2 hours. The reaction was cooled to room temperature, concentrated *in vacuo* to approximately 50 mL and filtered. The filtrate was concentrated to dryness *in vacuo*, the residue was triturated with dichloromethane and filtered to give the title compound as a white solid (6.2 g).

<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 5.92 (s, 2H), 7.40-7.47 (m, 1H), (d, 1H), 8.43 (dd, 1H), 9.58 (s, 1H).

LRMS (ES) 172 (M+H).

#### Preparation 89'

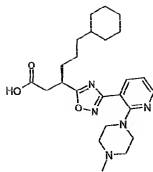
(3*R*)-3-[3-(2-Chloro-3-pyridinyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



The title compound was obtained as an off-white solid from the title compounds of Preparation 175 and Preparation 88', using a similar method to that described in Preparation 47'. Ester cleavage occurred upon flash chromatography on silica gel (graded elution of 2:1 to 1:1 hexane/ethyl acetate).

#### Preparation 90'

(3*R*)-6-Cyclohexyl-3-[3-[2-(4-methyl-1-piperazinyl)-3-pyridinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



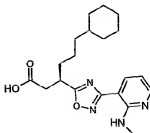
The title compound from Preparation 89' (0.4 g, 1.06 mmol) and *N*-methylpiperazine (4.0 mL, 36 mmol) were heated in a sealed reaction vessel at 100 °C for 8 hours. The reaction mixture was cooled to room temperature, dissolved in ethyl acetate (50 mL) then washed with 10% aqueous citric acid solution (20 mL), saturated aqueous sodium bicarbonate solution (20 mL) and water (20 mL). The aqueous citric acid washings were basified to pH7 with saturated aqueous sodium bicarbonate solution and then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo* to give the title compound as a brown oil (0.34 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.73-0.89 (m, 2H), 1.00-1.44 (m, 8H), 1.53-1.82 (m, 7H), 2.47 (s, 3H), 2.70 (dd, 1H), 2.77-2.97 (m, 5H), 3.13-3.38 (m, 4H), 3.38-3.52 (m, 1H), 6.86 (dd, 1H), 7.94 (d, 1H), 8.26 (dd, 1H), 9.80 (br s, 1H).

LRMS (TSP) 442 (M+H).

#### Preparation 91'

(3*R*)-6-Cyclohexyl-3-[(3-{2-(methylemino)-3-pyridinyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



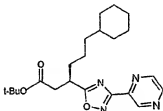
The title compound from Preparation 89' (0.5 g, 1.3 mmol) and methylamine (5.0 mL of 33% solution in ethanol, 50 mmol) were heated in a sealed reaction vessel at 100 °C for 3 hours. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was stirred in 10% aqueous citric acid solution (20 mL) for 30 minutes the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried (MgSO<sub>4</sub>), the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol 99:1 to 96:4) to give the title compound as a yellow oil (0.30 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.06-1.37 (m, 8H), 1.56-1.70 (m, 5H), 1.70-1.86 (m, 2H), 2.78 (dd, 1H), 2.99 (dd, 1H), 3.10 (s, 3H), 3.50-3.59 (m, 1H), 6.62 (dd, 1H), 7.15 (br s, 1H), 8.60 (br s, 1H).

LRMS (ES) 371 (M-H).

#### Preparation 92'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]hexanoate



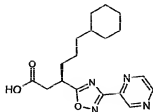
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and *N*-hydroxy-2-pyrazinecarboximidamide using a similar method to that described in Preparation 47, apart from the reaction solvent used was dichloromethane/dimethylformamide'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.87 (m, 2H), 1.03-1.47 (m, 17H), 1.57-1.69 (m, 5H), 1.69-1.93 (m, 2H), 2.71 (dd, 1H), 2.94 (dd, 1H), 3.54-3.61 (m, 1H), 8.62 (d, 1H), 8.66 (d, 1H), 9.38 (s, 1H).

LRMS (TSP) 401 (M+H).

#### Preparation 93'

(3*R*)-6-Cyclohexyl-3-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



5

The title compound was obtained as a yellow oil from the title compound of Preparation 92', using a similar method to that described in Preparation 31'.

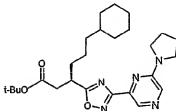
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.05-1.40 (m, 8H), 1.58-1.72 (m, 5H), 1.72-1.94 (m, 2H), 2.87 (dd, 1H), 3.12 (dd, 1H), 3.58-3.66 (m, 1H), 8.75 (d, 1H), 8.83 (d, 1H), 9.38 (s, 1H), 9.60 (br s, 1H).

10

LRMS (TSP) 345 (M+H).

## 15 Preparation 94'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-[6-(1-pyrrolidinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoate



20

The title compound was obtained as a yellow oil from the title compound from Preparation 175 and *N*'-hydroxy-6-(1-pyrrolidinyl)-2-pyrazinecarboximidamide (Pol. J. Pharmacol. 1977, 29, 61-68), using a similar method to that described in Preparation 47.

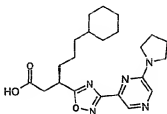
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.06-1.37 (m, 8H), 1.40 (s, 9H), 1.58-1.70 (m, 5H), 1.70-1.90 (m, 2H), 2.02-2.10 (m, 4H), 2.68 (dd, 1H), 2.89 (dd, 1H), 3.51-3.64 (m, 5H), 8.00 (s, 1H), 8.50 (s, 1H).

25

LRMS (ES) 492 (M+Na), 401 (M+H).

**Preparation 95'**

- 5 (3*R*)-6-Cyclohexyl-3-[3-(6-(1-pyrrolidinyl)-2-pyrazinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



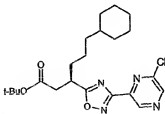
- 10 The title compound was obtained as a yellow oil from the title compound of Preparation 94', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.06-1.38 (m, 8H), 1.57-1.72 (m, 5H), 1.72-1.92 (m, 2H), 2.02-2.10 (m, 4H), 2.83 (dd, 1H), 3.07 (dd, 1H), 3.55-3.65 (m, 5H), 8.00 (s, 1H), 8.47 (s, 1H).

- 15 LRMS (ES) 436 (M+Na), 414 (M+H).

**Preparation 96'**

- 20 *tert*-Butyl (3*R*)-3-[3-(6-chloro-2-pyrazinyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl hexanoate



- 25 The title compound was obtained as a yellow oil from the title compound from Preparation 175 and 6-chloro-*N*-hydroxy-2-pyrazinecarboximidamide (Pol. J. Pharmacol. 1977, 29, 61-68), using a similar method to that described in Preparation 47'.



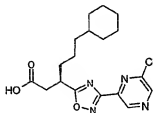
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.93 (m, 2H), 1.03-1.47 (m, 17H), 1.50-1.73 (m, 5H), 1.73-1.95 (m, 2H), 2.71 (dd, 1H), 2.93 (dd, 1H), 3.55-3.63 (m, 1H), 8.73 (d, 1H), 9.25 (s, 1H).

LRMS (ES) 891 (2M+Na), 457 (M+Na), 435 (M+H).

5

#### Preparation 97'

(3R)-3-[3-(6-Chloro-2-pyrazinyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl hexanoic acid



10

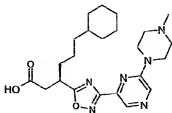
The title compound was obtained as a yellow oil from the title compound of Preparation 96', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.05-1.40 (m, 8H), 1.56-1.72 (m, 5H), 1.72-1.94 (m, 2H), 2.84 (dd, 1H), 3.08 (dd, 1H), 3.57-3.64 (m, 1H), 8.73 (s, 1H), 9.23 (s, 1H).

LRMS (ES) 401 (M+Na).

#### 20 Preparation 98'

(3R)-6-Cyclohexyl-3-[3-[6-(4-methyl-1-piperazinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



25

To a solution of the title compound from Preparation 97' (0.53 g, 1.4 mmol) in ethanol (5 mL) was added *N*-methylpiperazine (0.6 mL, 5.5 mmol) and the reaction was heated to 70 °C

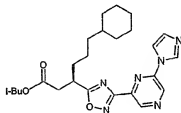
overnight. The solution was cooled to room temperature, the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo* to give the title compound as a yellow foam (0.66 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.04-1.43 (m, 8H), 1.56-1.86 (m, 7H), 2.47 (s, 3H), 2.65-2.90 (m, 5H), 2.96 (dd, 1H), 3.32-3.80 (m, 5H), 7.90 (s, 1H), 8.52 (s, 1H).

LRMS (ES) 465 (M+Na), 443 (M+H).

#### Preparation 99'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-{3-[6-(1*H*-imidazol-1-yl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl}hexanoate



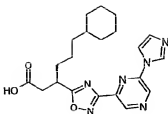
The title compound was obtained as a colourless oil as side-product during the formation of the title compound from Preparation 96'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.05-1.46 (m, 17H), 1.53-1.71 (m, 5H), 1.71-1.92 (m, 2H), 2.74 (dd, 1H), 2.92 (dd, 1H), 3.56-3.63 (m, 1H), 7.30 (s, 1H), 7.79 (s, 1H), 8.49 (s, 1H), 8.92 (s, 1H), 9.27 (s, 1H).

LRMS (ES) 489 (M+Na), 467 (M+H).

#### Preparation 100'

(3*R*)-6-Cyclohexyl-3-{3-[6-(1*H*-imidazol-1-yl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



The title compound was obtained as its trifluoroacetic acid salt, as an orange foam from the title compound of Preparation 99', using a similar method to that described in Preparation 31'.

5

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.91 (m, 2H), 1.04-1.44 (m, 8H), 1.57-1.74 (m, 5H), 1.74-1.95 (m, 2H), 2.90 (dd, 1H), 3.10 (dd, 1H), 3.60-3.69 (m, 1H), 7.58 (s, 1H), 8.07 (s, 1H), 9.21 (s, 1H), 9.44 (s, 1H), 9.63 (s, 1H).

10 LRMS (ES) 411 (M+H).

#### Preparation 101'

3-(4-Methyl-1-piperazinyl)-2-pyrazinecarbonitrile

15



To a solution of 3-cyano-2-chloropyrazine (0.45 g, 3.2 mmol) in methanol (10 mL) was added *N*-methylpiperazine (0.75 mL, 6.4 mmol) and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, then the residue was dissolved in ethyl acetate. The precipitate was filtered off and the filtrate was concentrated under reduce pressure. The residue was then purified by flash chromatography on silica gel (dichloromethane/methanol 95:5) to give the title compound as a yellow oil (0.59 g).

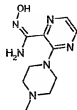
20

25 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 2.34 (s, 3H), 2.50-2.57 (m, 4H), 3.80-3.86 (m, 4H), 7.98 (d, 1H), 8.23 (dd, 1H).

LRMS (ES) 204 (M+H).

**Preparation 102'**

*N'*-Hydroxy-3-(4-methyl-1-piperazinyl)-2-pyrazinecarboximidamide



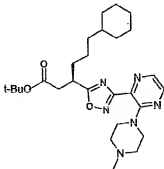
The title compound was obtained as a pale yellow solid from the title compound from Preparation 101', using a similar method to that described in Preparation 7'.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 2.18 (s, 3H), 2.32-2.39 (m, 4H), 3.35-3.41 (m, 4H), 5.75 (s, 2H), 7.91 (d, 1H), 8.10 (d, 1H), 9.56 (s, 1H).

LRMS (TSP) 237 (M+H).

**Preparation 103'**

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-[3-(4-methyl-1-piperazinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoate



The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the amidoxime from Preparation 102', using a similar method to that described in Preparation 47'.

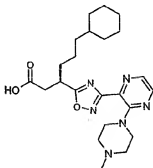
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.03-1.44 (m, 17H), 1.55-1.71 (m, 5H), 1.71-1.90 (m, 2H), 2.33 (s, 3H), 2.46-2.54 (m, 4H), 2.70 (dd, 1H), 2.91 (dd, 1H), 3.31-3.40 (m, 4H), 3.51-3.60 (m, 1H), 8.16 (d, 1H), 8.21 (d, 1H).

5

LRMS (ES) 499 (M+Na).

#### Preparation 104'

- 10 (3*R*)-6-Cyclohexyl-3-[3-[3-(4-methyl-1-piperazinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



- 15 The title compound was obtained as its trifluoroacetic acid salt, as a yellow foam from the title compound of Preparation 103', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.89 (m, 2H), 1.05-1.40 (m, 8H), 1.59-1.90 (m, 7H), 2.78-2.92 (m, 7H), 2.92-3.09 (m, 2H), 3.41-3.70 (m, 5H), 8.26 (s, 2H), 11.80 (br s, 1H).

20

LRMS (ES) 443 (M+H).

#### Preparation 105'

- 25 3-(4-Morpholinyl)-2-pyrazinecarbonitrile



To a solution of 3-cyano-2-chloropyrazine (0.7 g, 5.0 mmol) in methanol (20 mL) was added morpholine (1.0 mL, 11.0 mmol) and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, then the residue was dissolved in diethyl ether. The precipitate was filtered off and the filtrate was concentrated under reduce pressure to give the title compound as an orange solid (0.95 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.78-3.87 (m, 8H), 8.06 (d, 1H), 8.27 (d, 1H).

LRMS (TSP) 208 (M+Na), 191 (M+H).

#### Preparation 106\*

*N*-Hydroxy-3-(4-morpholinyl)-2-pyrazinecarboximidamide



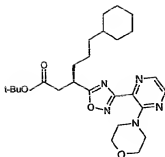
The title compound was obtained as a pale yellow solid from the title compound from Preparation 105', using a similar method to that described in Preparation 7'. The product was purified by flash chromatography on silica gel (dichloromethane/methanol 95:5 as eluant).

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 3.34-3.39 (m, 4H), 3.60-3.67 (m, 4H), 5.82 (s, 2H), 7.96 (d, 1H), 8.15 (d, 1H), 9.62 (s, 1H).

LRMS (TSP) 224 (M+H).

#### Preparation 107\*

*tert*-Butyl (3*R*)-6-cyclohexyl-3-{3-[3-(4-morpholinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl}hexanoate



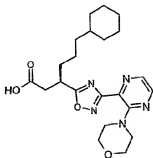
The title compound was obtained as an orange oil from the title compound from Preparation 175 and the amidoxime from Preparation 106', using a similar method to that described in Preparation 47'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.05-1.42 (m, 17H), 1.58-1.93 (m, 7H), 2.70 (dd, 1H), 2.91 (dd, 1H), 3.30-3.39 (m, 4H), 3.52-3.60 (m, 1H), 3.77-3.84 (m, 4H), 8.21 (d, 1H), 8.25 (d, 1H).

LRMS (ES) 508 (M+Na), 486 (M+H).

#### Preparation 108'

(3R)-6-Cyclohexyl-3-[3-[3-(4-morpholinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was obtained as a yellow foam from the title compound of Preparation 107', using a similar method to that described in Preparation 31'. The product was washed with saturated aqueous sodium bicarbonate solution to remove trifluoroacetic acid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.91 (m, 2H), 1.03-1.39 (m, 8H), 1.56-1.73 (m, 5H), 1.73-1.93 (m, 2H), 2.83 (dd, 1H), 3.09 (dd, 1H), 3.26-3.38 (m, 4H), 3.56-3.64 (m, 1H), 3.76-3.84 (m, 4H), 8.21 (d, 1H), 8.25 (d, 1H).

5 LRMS (ES) 430 (M+H).

#### Preparation 109'

3-(1-Pyrrolidinyl)-2-pyrazinecarbonitrile

10



To the title compound was obtained as a yellow solid from 2-chloro-3-cyanopyrazine and pyrrolidine, using a similar method to that described in Preparation 105'.

15

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.01-2.09 (m, 4H), 3.74-3.82 (m, 4H), 7.96 (d, 1H), 8.28 (d, 1H).

LRMS (ES) 197 (M+Na), 175 (M+H).

#### 20 Preparation 110'

N'-Hydroxy-3-(1-pyrrolidinyl)-2-pyrazinecarboximidamide



25

To a solution of hydroxylamine hydrochloride (0.24 g, 3.5 mmol) in methanol (30 mL) was added sodium metal (0.08 g, 3.5 mmol) portionwise. A solution of the title compound of Preparation 109' (0.60 g, 3.5 mmol) in methanol (10 mL) was added and the reaction was heated to reflux for 6 hours. The reaction was cooled to room temperature, the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was dried (MgSO<sub>4</sub>) and the

30



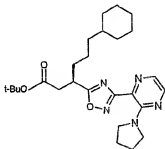
solvent was removed *in vacuo*. The residue was recrystallised from ethyl acetate to give the title compound as a yellow solid (0.32 g).

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 1.81-1.87 (m, 4H), 3.39-3.65 (m, 4H), 5.80 (s, 2H), 7.77 (d, 1H), 8.05 (d, 1H), 9.43 (s, 1H).

LRMS (ES) 230 (M+Na), 208 (M+H).

#### Preparation 111'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-[3-(1-pyrrolidinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoate



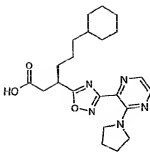
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the amidoxime from Preparation 110', using a similar method to that described in Preparation 47'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.07-1.47 (m, 17H), 1.58-1.93 (m, 11H), 2.69 (dd, 1H), 2.92 (dd, 1H), 3.23-3.34 (m, 4H), 3.51-3.59 (m, 1H), 7.99 (s, 1H), 8.17 (s, 1H).

LRMS (TSP) 471 (M+H).

#### Preparation 112'

(3*R*)-6-Cyclohexyl-3-[3-[3-(1-pyrrolidinyl)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl] hexanoic acid



The title compound was obtained as a yellow foam from the title compound of Preparation 111', using a similar method to that described in Preparation 31'.

5

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.91 (m, 2H), 1.06-1.40 (m, 8H), 1.57-1.95 (m, 11H), 2.82 (dd, 1H), 3.08 (dd, 1H), 3.22-3.33 (m, 4H), 3.56-3.63 (m, 1H), 8.00 (d, 1H), 8.17 (d, 1H).

LRMS (ES) 436 (M+Na), 414 (M+H).

10

#### Preparation 113'

3-(Dimethylamino)-2-pyrazinecarbonitrile



15

To the title compound was obtained as a yellow solid from 2-chloro-3-cyanopyrazine and dimethylamine (33% in ethanol), using a similar method to that described in Preparation 105'.

20  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.34 (s, 6H), 7.93 (d, 1H), 8.21 (d, 1H).

LRMS (ES) 149 (M+H).

#### Preparation 114'

25

3-(Dimethylamino)-N'-hydroxy-2-pyrazinecarboximidamide



The title compound was obtained as a pale yellow solid from the title compound of Preparation 113', using a similar method to that described in Preparation 110'.

5

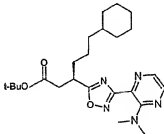
$^1\text{H}$  NMR (400 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$  2.97 (s, 6H), 5.78 (s, 2H), 7.82 (d, 1H), 8.06 (d, 1H), 9.49 (s, 1H).

LRMS (ES) 204 (M+Na), 182 (M+H).

10

#### Preparation 115'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(dimethylamino)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoate



15

The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the amidoxime from Preparation 114', using a similar method to that described in Preparation 47'.

20

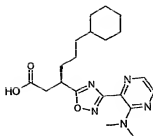
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.90 (m, 2H), 1.08-1.37 (m, 8H), 1.39 (s, 9H), 1.58-1.90 (m, 7H), 2.69 (dd, 1H), 2.87-2.98 (m, 7H), 3.51-3.59 (m, 1H), 8.07 (d, 1H), 8.17 (d, 1H).

LRMS (ES) 466 (M+Na), 444 (M+H).

25

#### Preparation 116'

(3*R*)-6-Cyclohexyl-3-[3-(dimethylamino)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was obtained as a yellow oil from the title compound of Preparation 115', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.89 (m, 2H), 1.05-1.40 (m, 8H), 1.55-1.70 (m, 5H), 1.70-1.93 (m, 2H), 2.82 (dd, 1H), 2.90 (s, 6H), 3.09 (dd, 1H), 3.53-3.61 (m, 1H), 8.06 (d, 1H), 8.17 (d, 1H).

LRMS (ES) 410 (M+Na), 388 (M+H).

#### Preparation 117'

*N*'-Hydroxy-3-(methylamino)-2-pyrazinecarboximidamide



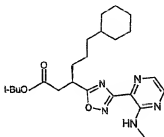
To a solution of 2-methylamino-3-cyanopyrazine (J. Heterocycl. Chem. 1992, 29, 1689-92) (0.37 g, 2.8 mmol) in methanol (10 mL) was added triethylamine (0.4 mL, 2.8 mmol) followed by hydroxylamine hydrochloride (0.19 g, 2.8 mmol) and the reaction was stirred at room temperature for 4 hours. The mixture was filtered, the filtrate was then evaporated to dryness. The residue was dissolved in ethyl acetate (50 mL) and washed with water (50 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo* to give the title compound as a white solid (0.45 g).

<sup>1</sup>H NMR (400 MHz, D<sub>6</sub>-DMSO) δ 2.93 (d, 3H), 5.95 (s, 2H), 7.77 (d, 1H), 8.06 (d, 1H), 8.34 (br, 1H), 10.20 (s, 1H).

LRMS (ES) 167 (M+H).

**Preparation 118'**

- 5 *tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(methylamino)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl)hexanoate



- 10 The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the amidoxime from Preparation 117', using a similar method to that described in Preparation 47'.

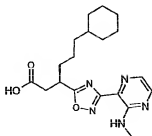
- 15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.92 (m, 2H), 1.04-1.40 (m, 17H), 1.58-1.80 (m, 6H), 1.80-1.93 (m, 1H), 2.70 (dd, 1H), 2.97 (dd, 1H), 3.15 (d, 3H), 3.54-3.61 (m, 1H), 8.03 (d, 1H), 8.20 (d, 1H).

LRMS (ES) 452 (M+Na), 430 (M+H).

**Preparation 119'**

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(3*R*)-6-Cyclohexyl-3-[3-(methylamino)-2-pyrazinyl]-1,2,4-oxadiazol-5-yl)hexanoic acid



- 25 The title compound was obtained as a yellow oil from the title compound of Preparation 118', using a similar method to that described in Preparation 31'.

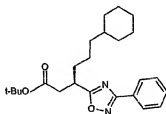
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.77-0.89 (m, 2H), 1.02-1.38 (m, 8H), 1.55-1.71 (m, 5H), 1.71-1.92 (m, 2H), 2.83 (dd, 1H), 3.05 (dd, 1H), 3.13 (d, 3H), 3.54-3.63 (m, 1H), 8.01 (d, 1H), 8.20 (d, 1H).

5 LRMS (ES) 396 ( $\text{M}+\text{Na}$ ), 374 ( $\text{M}+\text{H}$ ).

#### Preparation 120'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)hexanoate

10



The title compound was obtained as a yellow oil from the title compound from Preparation 175 and *N*'-hydroxybenzenecarboximidamide, using a similar method to that described in Preparation 47'.

15

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.92 (m, 2H), 1.06-1.45 (m, 17H), 1.58-1.88 (m, 7H), 2.68 (dd, 1H), 2.88 (dd, 1H), 3.46-3.58 (m, 1H), 7.43-7.53 (m, 3H), 8.05-8.12 (m, 2H).

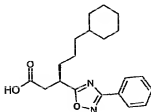
20

LRMS (TSP) 399 ( $\text{M}+\text{H}$ ).

#### Preparation 121'

(3*R*)-6-Cyclohexyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)hexanoic acid

25



The title compound was obtained as a colourless oil from the title compound of Preparation 120', using a similar method to that described in Preparation 31'.

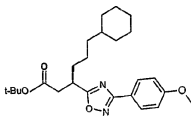
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.92 (m, 2H), 1.05-1.38 (m, 8H), 1.59-1.89 (m, 7H), 2.80 (dd, 5 1H), 3.05 (dd, 1H), 3.46-3.60 (m, 1H), 7.41-7.52 (m, 3H), 8.04-8.11 (m, 2H).

LRMS (TSP) 343 (M+H).

#### Preparation 122'

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*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]hexanoate



15 The title compound was obtained as a colourless oil from the title compound from Preparation 175 and *N*'-hydroxy-4-methoxybenzenecarboximidamide, using a similar method to that described in Preparation 49'.

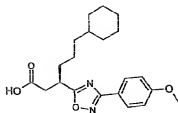
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.91(m, 2H), 1.08-1.47 (m, 17H), 1.57-1.90 (m, 7H), 2.66 (dd, 20 1H), 2.86 (dd, 1H), 3.46-3.58 (m, 1H), 3.85 (s, 3H), 6.97 (d, 2H), 8.00 (d, 2H).

LRMS (TSP) 428 (M).

#### Preparation 123'

25

(3*R*)-6-Cyclohexyl-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



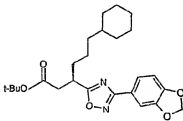
The title compound was obtained as a pale yellow oil from the title compound of Preparation 122', using a similar method to that described in Preparation 9'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.07-1.26 (m, 6H), 1.26-1.38 (m, 2H), 1.57-1.71 (m, 5H), 1.71-1.89 (m, 2H), 2.79 (dd, 1H), 3.02 (dd, 1H), 3.50-3.58 (m, 1H), 3.87 (s, 3H), 6.98 (d, 2H), 8.00 (d, 2H).

LRMS (ES) 373 (M+H).

#### Preparation 124'

*tert*-Butyl (3*R*)-3-[3-(1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl hexanoate



The title compound was obtained as a colourless oil from the title compound from Preparation 175 and *N*-hydroxy-1,3-benzodioxole-5-carboximidamide, using a similar method to that described in Preparation 47'.

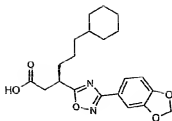
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.91 (m, 2H), 1.03-1.46 (m, 17H), 1.58-1.90 (m, 7H), 2.66 (dd, 1H), 2.86 (dd, 1H), 3.44-3.53 (m, 1H), 6.05 (s, 2H), 6.90 (d, 1H), 7.52 (s, 1H), 7.65 (d, 1H).

LRMS (TSP) 443 (M+H).

#### Preparation 125'

(3*R*)-3-[3-(1,3-Benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid





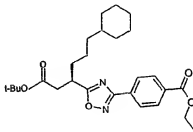
The title compound was obtained as a pale yellow oil from the title compound of Preparation 124', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.92 (m, 2H), 1.04-1.40 (m, 8H), 1.56-1.92 (m, 7H), 2.80 (dd, 1H), 3.03 (dd, 1H), 3.48-3.59 (m, 1H), 6.03 (s, 2H), 6.89 (d, 1H), 7.52 (s, 1H), 7.63 (d, 1H).

LRMS (TSP) 387 (M+H).

#### Preparation 126'

Ethyl 4-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl]benzoate



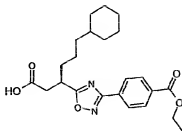
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and ethyl 4-[amino(hydroxyimino)methyl]benzoate (J. Med. Chem. 1972, 15, 1194), using a similar method to that described in Preparation 49'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.90 (m, 2H), 1.04-1.27 (m, 6H), 1.27-1.47 (m, 14H), 1.57-1.90 (m, 7H), 2.70 (dd, 1H), 2.88 (dd, 1H), 3.49-3.58 (m, 1H), 4.42 (q, 2H), 8.14 (s, 4H).

LRMS (ES) 472 (M+H).

#### Preparation 127'

(3*R*)-6-Cyclohexyl-3-[3-[4-(ethoxycarbonyl)phenyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



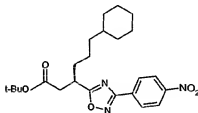
- 5 The title compound was obtained as a yellow oil from the title compound of Preparation 126', using a similar method to that described in Preparation 70'. The reaction was carried out using dichloromethane as a co-solvent.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.88 (m, 2H), 1.05-1.37 (m, 8H), 1.41 (t, 3H), 1.57-1.70 (m, 5H), 1.70-1.90 (m, 2H), 2.81 (dd, 1H), 3.03 (dd, 1H), 3.54-3.60 (m, 1H), 4.40 (q, 2H), 8.14 (s, 4H).

LRMS (ES) 415 (M+H).

#### 15 Preparation 128'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]hexanoate



20

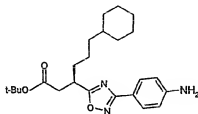
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and *N*-hydroxy-4-nitrobenzenecarboximidamide, using a similar method to that described in Preparation 49'. The cyclisation was carried out in toluene at 110 °C.

25 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.94 (m, 2H), 1.00-1.47 (m, 17H), 1.57-1.94 (m, 7H), 2.70 (dd, 1H), 2.88 (dd, 1H), 3.50-3.59 (m, 1H), 8.08 (d, 2H), 8.14 (d, 2H).

LRMS (TSP) 444 (M+H).

**Preparation 129'**

- 5 *tert*-Butyl (3*R*)-3-[3-(4-aminophenyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoate



- To a solution of the title compound from Preparation 128' (0.41 g, 0.9 mmol) in ethanol (20 mL) was added tin(II) chloride dihydrate (1.04 g, 4.6 mmol) and the reaction was heated to 70 °C for 3 hours. The mixture was cooled to room temperature, poured into saturated brine solution (30 mL) and then extracted with ethyl acetate (100 mL). The organic layer was washed with saturated brine solution (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (graded elution of hexane/ethyl acetate 90:10 to 50:50) to give the title compound as a pale yellow oil (0.28 g).
- 15

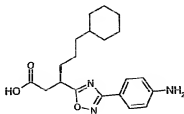
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.93 (m, 2H), 1.03-1.47 (m, 17H), 1.56-1.90 (m, 7H), 2.72 (dd, 1H), 2.81 (dd, 1H), 3.40-3.51 (m, 1H), 6.74 (d, 2H), 7.76 (d, 2H).

- 20 LRMS (TSP) 414 (M+H).

**Preparation 130'**

(3*R*)-3-[3-(4-Aminophenyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid

25



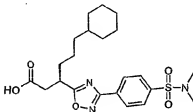
The title compound of Preparation 129' (0.63 g, 1.6 mmol) was dissolved in dichloromethane (15 mL) and trifluoroacetic acid (5 mL) and the reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was azeotroped with toluene and then dichloromethane. The residue was dissolved in ethyl acetate (100 mL) and then washed with saturated aqueous sodium dihydrogen citrate solution (100 mL) and saturated brine solution (100 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*, then the residue was purified by flash chromatography on silica gel (dichloromethane as eluant) to give the title compound as a white solid (0.07 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.91 (m, 2H), 1.07-1.40 (m, 8H), 1.58-1.70 (m, 5H), 1.70-1.90 (m, 2H), 2.81 (dd, 1H), 3.03 (dd, 1H), 3.48-3.57 (m, 1H), 6.72 (d, 2H), 7.85 (d, 2H).

LRMS (TSP) 358 (M+H).

#### 15 Preparation 131'

(3R)-6-Cyclohexyl-3-(3-{4-[(dimethylamino)sulfonyl]phenyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



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To a suspension of the title compound of Preparation 130' (0.13 g, 0.36 mmol) in glacial acetic acid (2.5 mL) and concentrated hydrochloric acid (2.5 mL) at -10 to -15 °C (ice-salt bath) was added sodium nitrite (0.04 g, 0.54 mmol) and the reaction was stirred at 0 °C for 1 hour. The mixture was then re-cooled to -10 to -15 °C and liquid sulfur dioxide was added (3-4 mL) followed by a solution of copper(II) chloride (0.14 g, 1.1 mmol) in water (approx 0.5 mL). The reaction was warmed to room temperature and stirred for 1 hour, then extracted with dichloromethane (20 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL), the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed *in vacuo*. The residue was azeotroped with toluene to remove acetic acid, then dissolved in dichloromethane (15 mL), cooled to 0 °C and dimethylamine (0.3 mL, 1.7 mmol) was added. The reaction was stirred at room temperature overnight, then the solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (20 mL) and saturated sodium bicarbonate solution (20 mL). The organic layer was washed with saturated sodium bicarbonate solution (2 x 20 mL),

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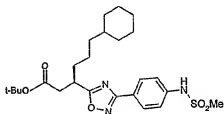
saturated brine solution (20 mL) then dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (graded elution of dichloromethane/methanol 100:0 to 99:1 to 98:2) to give the title compound as a yellow oil (0.07 g).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.77-0.90 (m, 2H), 1.03-1.39 (m, 8H), 1.58-1.73 (m, 5H), 1.73-1.92 (m, 2H), 2.72 (s, 6H), 2.81 (dd, 1H), 3.04 (dd, 1H), 3.54-3.61 (m, 1H), 7.89 (d, 2H), 8.25 (d, 2H).

LRMS (TSP) 450 (M+H).

#### Preparation 132'

*tert*-Butyl (3R)-6-cyclohexyl-3-(3-{4-[(methylsulfonyl)amino]phenyl}-1,2,4-oxadiazol-5-yl)hexanoate



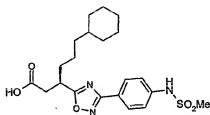
To a solution of the title compound from Preparation 129' (0.06 g, 0.14 mmol) in dichloromethane (10 mL) was added pyridine (0.013 mL, 0.16 mmol) and methanesulfonyl chloride (0.012 mL, 0.16 mmol). The reaction was heated to 40 °C then a solution of 4-dimethylaminopyridine (0.004 g, 0.03 mmol) in dichloromethane (5 mL) was added and the reaction was heated at reflux overnight. The mixture was cooled to room temperature, 1M aqueous hydrochloric acid (20 mL) was added, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (20 mL), saturated aqueous brine solution (20 mL) then dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (graded elution of hexane/ethyl acetate 90:10 to 70:30) to give the title compound as a colourless oil (0.06 g).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.92 (m, 2H), 1.07-1.44 (m, 17H), 1.60-1.90 (m, 7H), 2.68 (dd, 1H), 2.86 (dd, 1H), 3.08 (s, 3H), 3.46-3.58 (m, 1H), 7.07 (s, 1H), 7.32 (d, 2H), 8.07 (d, 2H).

LRMS (ES) 514 (M+Na), 492 (M+H).

**Preparation 133'**

- 5 (3*R*)-6-Cyclohexyl-3-(3-{4-[(methylsulfonyl)amino]phenyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



- 10 The title compound was obtained as a white foam from the title compound of Preparation 132', using a similar method to that described in Preparation 130'.

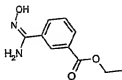
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.90 (m, 2H), 1.00-1.38 (m, 8H), 1.58-1.86 (m, 7H), 2.74-2.82 (m, 1H), 2.92-3.08 (m, 4H), 3.46-3.58 (m, 1H), 7.20 (d, 2H), 7.65 (br s, 1H), 7.94 (d, 2H).

- 15 LRMS (TSP) 436 (M+H).

**Preparation 134'**

Ethyl 3-[amino(hydroxyimino)methyl]benzoate

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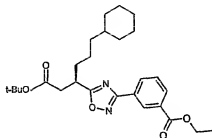
The title compound was obtained as a white solid from ethyl-(3-cyanophenyl)-carboxylate, using a similar method to that described in Preparation 117'.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 1.40 (t, 3H), 4.38 (q, 2H), 7.50 (dd, 1H), 7.85 (d, 1H), 8.06 (d, 1H), 8.32 (s, 1H).

LRMS (ES) 209 (M+H).

**Preparation 135'**

Ethyl 3-[5-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl]benzoate



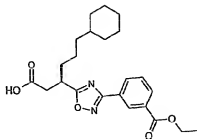
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the amidoxime from Preparation 134', using a similar method to that described in Preparation 47'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.91 (m, 2H), 1.04-1.45 (m, 20H), 1.55--1.93 (m, 7H), 2.69 (dd, 1H), 2.88 (dd, 1H), 3.48-3.59 (m, 1H), 4.42 (q, 2H), 7.57 (dd, 1H), 8.18 (d, 1H), 8.26 (d, 1H), 8.74 (s, 1H).

LRMS (ES) 452 (M+Na), 430 (M+H).

**Preparation 136'**

(3*R*)-6-Cyclohexyl-3-[3-[3-(ethoxycarbonyl)phenyl]-1,2,4-oxadiazol-5-yl]hexanoic acid



The title compound was obtained as a yellow oil from the title compound of Preparation 135', using a similar method to that described in Preparation 70'. The reaction was carried out using dichloromethane as a co-solvent.

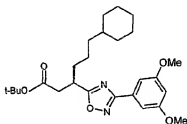
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.91 (m, 2H), 1.04-1.45 (m, 11H), 1.55-1.70 (m, 5H), 1.70-1.93 (m, 2H), 2.81 (dd, 1H), 3.06 (dd, 1H), 3.52-3.62 (m, 1H), 4.42 (q, 2H), 7.57 (dd, 1H), 8.18 (d, 1H), 8.24 (d, 1H), 8.74 (s, 1H).

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LRMS (TSP) 414 (M).

#### Preparation 137'

10 *tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]hexanoate



The title compound was obtained as a colourless oil from the title compound from Preparation 175 and *N*-hydroxy-3,5-dimethoxybenzenecarboximidamide, using a similar method to that described in Preparation 47'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.04-1.25 (m, 6H), 1.27-1.36 (m, 2H), 1.39 (s, 9H), 1.58-1.89 (m, 7H), 2.69 (dd, 1H), 2.88 (dd, 1H), 3.48-3.57 (m, 1H), 3.85 (s, 6H), 6.59 (s, 1H), 7.24 (s, 2H).

20

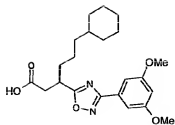
LRMS (TSP) 459 (M+H).

#### Preparation 138'

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(3*R*)-6-Cyclohexyl-3-[3-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]hexanoic acid





The title compound was obtained as a white solid from the title compound of Preparation 137', using a similar method to that described in Preparation 31'.

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<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.91 (m, 2H), 1.02-1.26 (m, 6H), 1.26-1.40 (m, 2H), 1.58-1.70 (m, 5H), 1.70-1.90 (m, 2H), 2.80 (dd, 1H), 3.05 (dd, 1H), 3.50-3.59 (m, 1H), 3.85 (s, 6H), 6.59 (s, 1H), 7.24 (s, 2H).

10 LRMS (TSP) 403 (M+H).

#### Preparation 139'

*N*-Hydroxy-1*H*-pyrazole-4-carboximidamide

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The title compound was obtained as a white solid from 4-cyanopyrazole using a similar method to that described in Preparation 110'.

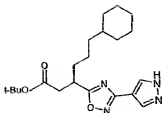
20

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 5.60 (br s, 2H), 7.67 (br s, 1H), 7.93 (br s, 1H), 9.07 (br s, 1H), 12.85 (br s, 1H).

#### Preparation 140'

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*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(1*H*-pyrazol-4-yl)-1,2,4-oxadiazol-5-yl]hexanoate



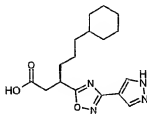
The title compound was obtained as a yellow oil from the title compound from Preparation 175 and the amidoxime from Preparation 139', using a similar method to that described in Preparation 47'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.91 (m, 2H), 1.05-1.47 (m, 17H), 1.58-1.87 (m, 7H), 2.67 (dd, 1H), 2.85 (dd, 1H), 3.46-3.54 (m, 1H), 7.98 (s, 1H), 8.15 (s, 2H).

LRMS (TSP) 389 (M+H).

#### Preparation 141'

(3R)-6-Cyclohexyl-3-[3-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-5-yl]hexanoic acid



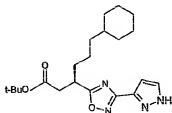
The title compound was obtained as a white solid from the title compound of Preparation 140', using a similar method to that described in Preparation 31'. The product was purified by flash chromatography on silica gel (dichloromethane/methanol 92.5:7.5 as eluant).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.77-0.93 (m, 2H), 1.02-1.43 (m, 8H), 1.51-1.92 (m, 7H), 2.82 (dd, 1H), 3.02 (dd, 1H), 3.47-3.59 (m, 1H), 8.09 (s, 2H).

LRMS (TSP) 332 (M).

#### Preparation 142'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]hexanoate



- 5 The title compound was obtained as a colourless oil from the title compound from Preparation 175 and *N*-hydroxy-1*H*-pyrazole-3-carboximidamide, using a similar method to that described in Preparation 47'.

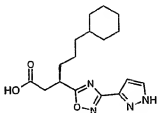
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.95 (m, 2H), 1.02-1.48 (m, 17H), 1.57-1.91 (m, 7H), 2.69 (dd, 1H), 2.90 (dd, 1H), 3.48-3.60 (m, 1H), 6.94 (s, 1H), 7.13 (s, 1H), 7.77 (s, 1H).

LRMS (ES) 389 (M+H).

#### Preparation 143'

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(3*R*)-6-Cyclohexyl-3-[3-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]hexanoic acid



- 20 The title compound was obtained as a colourless oil from the title compound of Preparation 142', using a similar method to that described in Preparation 31'.

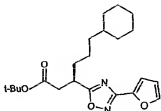
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.75-0.93 (m, 2H), 1.00-1.40 (m, 8H), 1.51-1.90 (m, 7H), 2.81 (dd, 1H), 3.01 (dd, 1H), 3.48-3.65 (m, 1H), 6.80-7.00 (br s, 1H), 7.60-7.80 (br s, 1H).

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LRMS (TSP) 333 (M+H).

#### Preparation 144'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(2-furyl)-1,2,4-oxadiazol-5-yl]hexanoate



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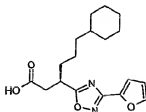
The title compound was obtained as a colourless oil from the title compound from Preparation 175 and *N*-hydroxy-2-furancarboximidamide (US 3767646), using a similar method to that described in Preparation 47'.

- 10 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.89 (m, 2H), 1.05-1.44 (m, 17H), 1.57-1.88 (m, 7H), 2.66 (dd, 1H), 2.85 (dd, 1H), 3.47-3.56 (m, 1H), 6.56 (d, 1H), 7.12 (d, 1H), 7.60 (s, 1H).

LRMS (ES) 389 (M+H).

15 **Preparation 145'**

(3*R*)-6-Cyclohexyl-3-[3-(2-furyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



20

The title compound was obtained as a colourless oil from the title compound of Preparation 144', using a similar method to that described in Preparation 31'.

- 25 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.93 (m, 2H), 1.05-1.39 (m, 8H), 1.58-1.89 (m, 7H), 2.81 (dd, 1H), 3.03 (dd, 1H), 3.52-3.61 (m, 1H), 6.57 (d, 1H), 7.14 (d, 1H), 7.62 (s, 1H).

LRMS (TSP) 333 (M+H).

**Preparation 146'***N'*-Hydroxy-3-quinolinecarboximidamide

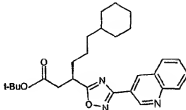
5

The title compound was obtained as a white solid from 3-cyanoquinoline using a similar method to that described in Preparation 110'.

- 10 <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O-DMSO) δ 6.06 (s, 2H), 7.62 (dd, 1H), 7.76 (dd, 1H), 7.96 (d, 1H), 8.02 (d, 1H), 8.56 (d, 1H), 9.12 (d, 1H), 9.97 (s, 1H).

**Preparation 147'**

- 15 *tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(3-quinolinyl)-1,2,4-oxadiazol-5-yl]hexanoate



- 20 The title compound was obtained as a clear oil from the title compound from Preparation 175 and the amidoxime from Preparation 146', using a similar method to that described in Preparation 49'.

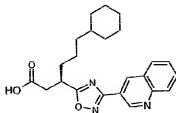
- 25 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.80-0.92 (m, 2H), 1.09-1.26 (m, 6H), 1.31-1.44 (m, 11H), 1.58-1.71 (m, 5H), 1.71-1.92 (m, 2H), 2.73 (dd, 1H), 2.92 (dd, 1H), 3.54-3.62 (m, 1H), 7.63 (dd, 1H), 7.80 (dd, 1H), 7.94 (d, 1H), 8.17 (d, 1H), 8.86 (d, 1H), 9.55 (d, 1H).

LRMS (TSP) 450 (M).

**Preparation 148'**

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(3*R*)-6-Cyclohexyl-3-[3-(3-quinolinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



5 The title compound was obtained as a colourless oil from the title compound of Preparation 147', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.75-0.96 (m, 2H), 1.04-1.42 (m, 8H), 1.54-1.74 (m, 5H), 1.74-1.95 (m, 2H), 2.86 (dd, 1H), 3.07 (dd, 1H), 3.55-3.67 (m, 1H), 7.78 (dd, 1H), 7.97 (dd, 1H), 8.07 (d, 1H), 8.40 (d, 1H), 9.17 (d, 1H), 9.68 (d, 1H).

LRMS (ES) 394 (M+H).

#### Preparation 149'

15

*N*'-Hydroxy-1-isoquinolinecarboximidamide



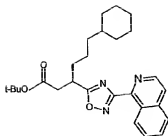
20 The title compound was obtained as a white solid from 1-cyanoisoquinoline using a similar method to that described in Preparation 110'.

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O-DMSO) δ 5.94 (s, 2H), 7.67 (dd, 1H), 7.78 (dd, 1H), 7.86 (d, 1H), 7.99 (d, 1H), 8.52 (d, 1H), 9.07 (d, 1H), 10.11 (s, 1H).

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#### Preparation 150'

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(1-isoquinolinyl)-1,2,4-oxadiazol-5-yl]hexanoate



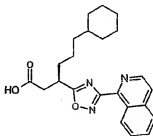
The title compound was obtained as a colourless oil from the title compound from Preparation 175 and the amidoxime from Preparation 149', using a similar method to that described in Preparation 49'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.95 (m, 2H), 1.04-1.48 (m, 17H), 1.50-1.74 (m, 5H), 1.74-2.00 (m, 2H), 2.75 (dd, 1H), 3.00 (dd, 1H), 3.60-3.71 (m, 1H), 7.65-7.85 (m, 3H), 7.92 (d, 1H), 8.77 (d, 1H), 8.98 (d, 1H).

LRMS (TSP) 451 (M+H).

#### Preparation 151'

(3R)-6-Cyclohexyl-3-[3-(1-isoquinolinyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



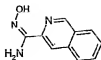
The title compound was obtained as a colourless oil from the title compound of Preparation 150', using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.95 (m, 2H), 1.03-1.49 (m, 8H), 1.55-1.74 (m, 5H), 1.74-2.00 (m, 2H), 2.89 (dd, 1H), 3.20 (dd, 1H), 3.64-3.74 (m, 1H), 7.80 (dd, 1H), 7.89 (dd, 1H), 7.95-8.06 (m, 2H), 8.80 (d, 1H), 9.09 (d, 1H).

LRMS (ES) 394 (M+H).

**Preparation 152'**

*N*'-Hydroxy-3-isoquinolinecarboximidamide

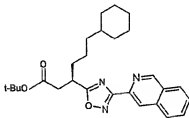


The title compound was obtained as a white solid from 3-cyanoisoquinoline using a similar method to that described in Preparation 110'.

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O-DMSO) δ 5.93 (s, 2H), 7.67 (dd, 1H), 7.78 (dd, 1H), 8.03 (d, 1H), 8.14 (d, 1H), 8.29 (s, 1H), 9.33 (s, 1H), 9.78 (s, 1H).

**Preparation 153'**

*tert*-Butyl (3*R*)-6-cyclohexyl-3-[3-(3-isoquinoliny)-1,2,4-oxadiazol-5-yl]hexanoate



The title compound was obtained as a colourless oil from the title compound from Preparation 175 and the amidoxime from Preparation 152', using a similar method to that described in Preparation 49'.

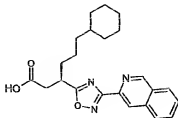
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.93 (m, 2H), 1.04-1.47 (m, 17H), 1.52-1.71 (m, 5H), 1.71-1.97 (m, 2H), 2.72 (dd, 1H), 2.94 (dd, 1H), 3.56-3.64 (m, 1H), 7.71 (dd, 1H), 7.78 (dd, 1H), 7.94 (d, 1H), 8.07 (d, 1H), 8.75 (s, 1H), 9.40 (s, 1H).

LRMS (TSP) 450 (M+H).

**Preparation 154'**



(3*R*)-6-Cyclohexyl-3-[3-(3-isoquinoliny)-1,2,4-oxadiazol-5-yl]hexanoic acid



5

The title compound was obtained as a white solid from the title compound of Preparation 153', using a similar method to that described in Preparation 31'. The product was purified by flash chromatography on silica gel (dichloromethane/methanol 96:4 as eluant).

10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-0.93 (m, 2H), 1.00-1.44 (m, 8H), 1.50-1.72 (m, 5H), 1.72-1.98 (m, 2H), 2.97 (dd, 1H), 3.18 (dd, 1H), 3.60-3.70 (m, 1H), 7.70 (dd, 1H), 7.78 (dd, 1H), 7.94 (d, 1H), 8.05 (d, 1H), 8.52 (s, 1H), 9.40 (s, 1H).

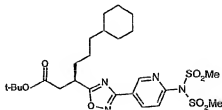
LRMS (ES) 809 (2M+Na, 30%), 416 (M+Na), 394 (M+H).

15

#### Preparation 155'

*tert*-Butyl (3*R*)-3-[3-[6-bis(methylsulfonyl)amino]-3-pyridinyl]-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoate

20



To a solution of the title compound from Preparation 58' (0.16 g, 0.4 mmol) and triethylamine (0.22 mL, 1.5 mmol) in 1,1,1-trichloroethane (10 mL) was added methanesulfonyl chloride (0.12 mL, 1.5 mmol) and the reaction was heated to 70 °C overnight. The reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (10 mL) and washed with 1M hydrochloric acid solution (10 mL). The aqueous layer was basified to pH 10 and then extracted with dichloromethane (10 mL). The combined

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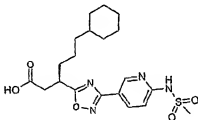
organic extracts were dried ( $\text{MgSO}_4$ ) and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 3:1 as eluant) to give the title compound as a yellow solid (0.14 g).

- 5  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.90 (m, 2H), 1.07-1.38 (m, 8H), 1.39 (s, 9H), 1.53-1.87 (m, 7H), 2.68 (dd, 1H), 2.86 (dd, 1H), 3.48-3.62 (m, 7H), 7.43 (d, 1H), 8.50 (d, 1H), 9.24 (s, 1H).

LRMS (ES) 593 (M+Na), 571 (M+H).

10 **Preparation 156'**

(3*R*)-6-Cyclohexyl-3-(3-(6-((methylsulfonyl)amino)-3-pyridinyl)-1,2,4-oxadiazol-5-yl)hexanoic acid



15

The title compound Preparation 155' (0.14 g, 0.25 mmol) was heated in a mixture of dioxane (5 mL) and 1M aqueous sodium hydroxide solution (5 mL) for 2 hours. The reaction was cooled to room temperature and washed with 2M hydrochloric acid solution (5 mL) and water (5 mL). The organic layer was dried ( $\text{MgSO}_4$ ) and the solvent was removed in vacuo to give the title compound as a white solid (0.08 g).

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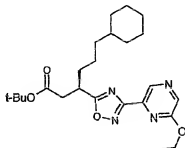
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.78-0.93 (m, 2H), 1.07-1.38 (m, 8H), 1.56-1.70 (m, 5H), 1.70-1.84 (m, 2H), 2.78 (dd, 1H), 2.92 (dd, 1H), 3.28 (s, 3H), 3.48-3.58 (m, 1H), 7.14 (d, 1H), 8.26 (d, 1H), 8.83 (s, 1H).

25

LRMS (ES) 459 (M+Na), 437 (M+H).

**PREPARATION 157'**

TERT-BUTYL(3R)-6-CYCLOHEXYL-3-[3-(6-ETHOXY-2-PYRAZINYL)-1,2,4-OXADIAZOL-5-YL]HEXANOATE



5

The title compound was obtained as a colourless oil from the compound of Preparation 175' and 3-ethoxy-N'-hydroxy-2-pyrazinecarboximidamide; using a similar method to that described in Preparation 47'.

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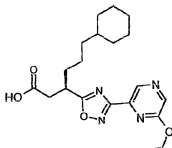
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.88 (m, 2H), 1.07-1.24 (m, 6H), 1.24-1.34 (m, 2H), 1.40 (s, 9H), 1.44 (t, 3H), 1.58-1.70 (m, 5H), 1.71-1.92 (m, 2H), 2.72 (dd, 1H), 2.92 (dd, 1H), 3.58 (m, 1H), 4.53 (q, 2H), 8.35 (s, 1H), 8.86 (s, 1H).

15 LRMS (TSP) 455 (M+H).

**PREPARATION 158'**

(3R)-6-CYCLOHEXYL-3-[3-(6-ETHOXY-2-PYRAZINYL)-1,2,4-OXADIAZOL-5-YL]HEXANOIC ACID

20



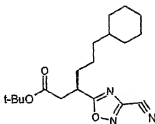
The title compound was obtained as a colourless gum from the compound of Preparation 157'; using a similar method to that described in Preparation 31'.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.88 (m, 2H), 1.07-1.24 (m, 6H), 1.24-1.34 (m, 2H), 1.44 (t, 3H), 1.58-1.70 (m, 5H), 1.71-1.92 (m, 2H), 2.82 (dd, 1H), 3.05 (dd, 1H), 3.58 (m, 1H), 4.53 (q, 2H), 8.35 (s, 1H), 8.86 (s, 1H).

LRMS (ES) 389 (M+H), 411 (M+Na).

#### PREPARATION 159<sup>1</sup>

TERT-BUTYL(3R)-3-(3-CYANO-1,2,4-OXADIAZOL-5-YL)-6-CYCLOHEXYLHEXANOATE



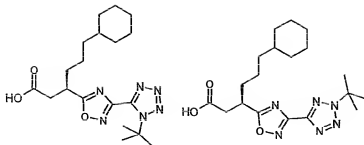
Trifluoroacetic anhydride (0.4 mL, 2.88 mmol) was added dropwise to a cooled solution of the title compound from Preparation 179 (1.0 g, 2.74 mmol) in dichloromethane (20 mL): pyridine (0.44 mL, 5.48 mmol). The reaction flask was stirred at 0 °C for 1 hour. The reaction was diluted with dichloromethane (10 mL) and washed with 5% citric acid (3 x 20 mL). The combined organic layers were dried (MgSO<sub>4</sub>), the solvent was removed in vacuo to give the title compound as a colourless oil (0.863 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.79-0.94 (m, 2H), 1.08-1.39 (m, 8H), 1.41 (s, 9H), 1.60-1.85 (m, 7H), 2.70 (dd, 1H), 2.90 (dd, 1H), 3.53 (m, 1H).

LRMS (ES) 370 (M+Na).

#### PREPARATION 160<sup>1</sup>

(3R)-3-[3-(1-TERT-BUTYL-1H-TETRAAZOL-5-YL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYLHEXANOIC ACID AND (3R)-3-[3-(2-TERT-BUTYL-2H-TETRAAZOL-5-YL)-1,2,4-OXADIAZOL-5-YL]-6-CYCLOHEXYLHEXANOIC ACID



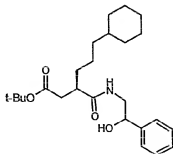
To a solution of the title compound from Preparation 159' (0.85 g, 2.45 mmol) in toluene (8 mL) was added trimethylsilyl azide (0.65 mL, 4.90 mmol) and dibutyltin oxide (0.1 g, 0.245 mmol). The reaction was heated at 100 °C for 24 hours under nitrogen, then the solvent was removed in vacuo. The residue was acidified with 2N hydrochloric acid (pH1), diluted with water (2 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried (MgSO<sub>4</sub>), the solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (graded elution of dichloromethane to dichloromethane/methanol 98:2) to give the title compounds, a 1:1 mixture of isomers, as a yellow oil (0.520 g).

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 0.80-0.92 (m, 4H), 1.05-1.40 (m, 18H), 1.52-1.73 (m, 22H), 1.75-1.94 (m, 8H), 2.84 (m, 2H), 3.05 (m, 2H), 3.62 (m, 2H).

LRMS (ES) 389 (M-H).

#### PREPARATION 161'

TERT-BUTYL(3R)-6-CYCLOHEXYL-3-((2-HYDROXY-2-PHENYLETHYL)AMINO)CARBONYLHEXANOATE



To a solution of the title compound from Preparation 175 (0.50 g, 1.86 mmol) in dichloromethane (15 mL) was added 1-hydroxybenzotriazole (0.294 g, 2.18 mmol), 1-(3-dimethylaminopropyl)-3-

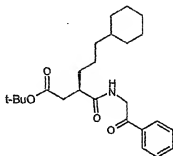
ethylcarbodiimide hydrochloride (0.418 g, 2.18 mmol) and 2-amino-1-phenylethanol (0.3 g, 2.18 mmol). The reaction was stirred at room temperature for 24 hours and then the solvent was removed in vacuo. The residue was diluted in ethyl acetate (150 mL) and washed with 10% citric acid (100 mL), water (100 mL), saturated sodium bicarbonate solution (100 mL) and brine (100 mL).  
5 The organic layer was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (graded elution of ethyl acetate/hexane 10:90 to 50:50) to give the title compound as an oil (0.668 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.88 (m, 2H), 1.06-1.50 (m, 8H), 1.42 (s, 9H), 1.45-1.77 (m, 7H), 2.31-2.58 (m, 2H), 2.58-2.78 (m, 1H), 3.18 (m, 0.5H), 3.40 (m, 0.5H), 3.80-3.84 (m, 2H), 4.88 (m, 1H), 6.13 (m, 1H), 7.25-7.42 (m, 5H).

LRMS (TSP) 418 (M+H).

## 15 PREPARATION 162'

TERT-BUTYL(3R)-6-CYCLOHEXYL-3-((2-OXO-2-PHENYLETHYL)AMINO)CARBONYLHEXANOATE



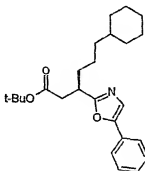
To a solution of the title compound from Preparation 161' (0.3 g, 0.72 mmol) in anhydrous dichloromethane (10 mL) was added 'Dess-Martin periodinane' (0.366 g, 0.86 mmol). The reaction was stirred at room temperature for 1.5 hours, then diluted with dichloromethane (25 mL). The reaction was treated with 20% sodium thiosulphate solution (6 mL) and saturated  
25 aqueous sodium bicarbonate solution (10 mL) and stirred for 10 mins. The layers were separated and aqueous layer extracted with dichloromethane (25 mL). The combined organic layers were washed with water, brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (graded elution of ethyl acetate/hexane 5:95 to 20:80) to give the title compound as an oil (0.205 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-0.95 (m, 2H), 1.05-1.51 (m, 8H), 1.40 (s, 9H), 1.54-1.80 (m, 7H), 2.31-2.42 (m, 1H), 2.60-2.78 (m, 2H), 4.68-4.88 (m, 2H), 6.70 (m, 1H), 7.50 (m, 2H), 7.60 (t, 1H), 7.97 (d, 2H).

5 LRMS (TSP) 416 (M+H).

#### PREPARATION 163'

##### TERT-BUTYL (3R)-6-CYCLOHEXYL-3-(5-PHENYL-1,3-OXAZOL-2-YL)HEXANOATE



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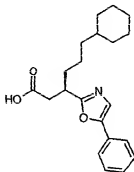
Trifluoromethanesulphonic anhydride (0.182 mL, 1.08 mmol) was added to a solution of triphenylphosphine oxide (0.603 g, 2.17 mmol) in dichloromethane (9 mL) at 0 °C under nitrogen. The reaction was stirred for 15 mins at 0 °C until a white precipitate was formed. A solution of the title compound from Preparation 162' (0.150 g, 0.36 mmol) in anhydrous dichloromethane (3 mL) was then added to the reaction, followed by triethylamine (0.2 mL, 1.44 mmol). After stirring for 10 mins the reaction was diluted with ethyl acetate (100 mL) and washed with 10% aqueous citric acid solution (50 mL), saturated aqueous sodium bicarbonate solution (50 mL) and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (hexane/diethyl ether 2:1 as eluant) to give the title compound as colourless oil (0.104 g).

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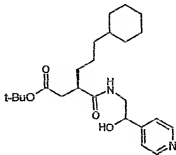
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-0.95 (m, 2H), 1.05-1.48 (m, 8H), 1.40 (s, 9H), 1.60-1.88 (m, 7H), 2.60 (dd, 1H), 2.80 (dd, 1H), 3.40 (m, 1H), 7.20-7.37 (m, 2H), 7.40 (t, 2H), 7.62 (d, 2H).

25 LRMS (TSP) 398 (M+H).

**PREPARATION 164****(3R)-6-CYCLOHEXYL-3-(5-PHENYL-1,3-OXAZOL-2-YL)HEXANOIC ACID**

- 5 The title compound was obtained as a colourless oil (0.172 g) from the compound of Preparation 163 using a similar method to that described in Preparation 19'. The residue was dissolved in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL) then water (2 x 50 mL). The organic solution was dried ( $\text{MgSO}_4$ ) and then concentrated in vacuo.
- 10  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.76-0.95 (m, 2H), 1.02-1.48 (m, 6H), 1.57-1.84 (m, 7H), 2.57 (dd, 1H), 2.96 (dd, 1H), 3.45 (m, 1H), 7.22-7.34 (d, 2H), 7.42 (t, 2H), 7.62 (d, 2H).

LRMS (TSP) 342 (M+H).

**15 PREPARATION 165'****TERT-BUTYL(3R)-6-CYCLOHEXYL-3-((1-HYDROXY(4-PYRIDINYLMETHYL)AMINO)CARBONYL)HEXANOATE**

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The title compound was obtained as a colourless oil (0.856 g) from the compound of Preparation 175' and 2-amino-1-(4-pyridinyl)ethanol (Ref; Burus; Powell;



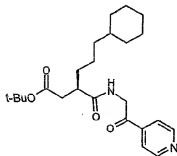
J.Amer.Chem.Soc.;67;1945;1468,1472;); using a similar method to that described in Preparation 161'. N,N-Dimethylformamide was added to the reaction and heated to 40 °C for 16 hours.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.98 (m, 2H), 1.04-1.50 (m, 8H), 1.41 (s, 9H), 1.52-1.84 (m, 6H), 2.28-2.78 (m, 3H), 3.06 (m, 1H), 3.38-3.48 (m, 1H), 3.65 (m, 0.5H), 3.82 (m, 0.5H), 4.30-4.65 (br d, 1H), 4.90 (m, 1H), 6.28 (m, 1H), 7.31 (m, 2H), 8.56 (m, 2H).

LRMS (TSP) 418 (M+).

#### 10 PREPARATION 166'

TERT-BUTYL(3R)-6-CYCLOHEXYL-3-[(ISONICOTINOYLAMINO)CARBONYL]HEXANOATE



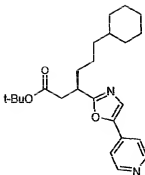
The title compound was obtained as a colourless oil from the title compound of Preparation 165'; using a similar method to that described in Preparation 162'. The residue was purified by flash chromatography on silica gel (ethyl acetate/methanol 98:2 as eluant).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.70-0.96 (m, 2H), 0.98-1.51 (m, 8H), 1.40 (s, 9H), 1.50-1.74 (m, 6H), 2.30-2.41 (m, 1H), 2.57-2.78 (m, 2H), 4.82-4.88 (m, 2H), 6.70 (m, 1H), 7.70 (m, 2H), 8.82 (m, 2H).

LRMS (TSP) 416 (M+).

#### PREPARATION 167'

TERT-BUTYL (3R)-6-CYCLOHEXYL-3-[5-(4-PYRIDINYL)-1,3-OXAZOL-2-YL]HEXANOATE



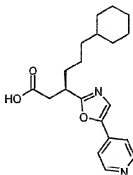
The title compound was obtained as a colourless oil from the compound of Preparation 166'; using a similar method to that described in Preparation 163'. The reaction was stirred for 2 hours after the addition of triethylamine and was purified by flash chromatography (eluting with ethyl acetate:hexane 1:1).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.74-0.96 (m, 2H), 1.00-1.48 (m, 8H), 1.34 (s, 9H), 1.55-1.90 (m, 7H), 2.60 (dd, 1H), 2.80 (dd, 1H), 3.40 (m, 1H), 7.44 (m, 3H), 7.62 (d, 2H).

LRMS (TSP) 399 (M+H).

#### PREPARATION 168'

(3R)-6-Cyclohexyl-3-[5-(4-pyridinyl)-1,3-oxazol-2-yl]hexanoic acid



The title compound was obtained as a colourless oil (0.14g) from the compound of Preparation 167' (0.17g) using a similar method to that described in Preparation 19'. The residue was recrystallised from hexane/ethyl acetate. The yellow solid was then dissolved in saturated aqueous sodium bicarbonate (50 mL) and acidified to pH 4.0 with 10% citric acid solution. The aqueous layer was extracted with ethyl acetate (2 x 50 mL), dried ( $\text{MgSO}_4$ ) and then concentrated in vacuo.

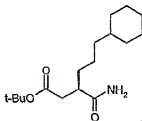
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.94 (m, 2H), 1.04-1.46 (m, 8H), 1.58-1.90 (m, 7H), 2.80 (dd, 1H), 2.98 (dd, 1H), 3.45 (m, 1H), 7.74 (s, 1H), 7.80 (d, 2H), 8.80 (d, 2H).

LRMS (TSP) 342 (M+).

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#### PREPARATION 169'

TERT-BUTYL(3R)-3-(AMINOCARBONYL)-6-CYCLOHEXYLHEXANOATE



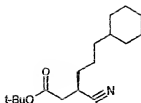
- 10 To a solution of the title compound from Preparation 175' (0.60 g, 0.2 mmol) in dichloromethane (20 mL) was added N-methylmorpholine (0.22 mL, 0.201 mmol). The reaction was cooled to 0 °C in an ice bath, then iso-butylchloroformate (0.27 mL, 0.207 mmol). The mixture was stirred for 1 hour, then ammonia gas was bubbled through the reaction until saturated. The reaction was warmed to room temperature and stirred for 45 mins. The reaction was diluted with
- 15 dichloromethane (50 mL) and washed with 5% aqueous citric acid solution (25 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride (30 mL), brine and dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (graded elution of ethyl acetate/hexane 1:9 to 1:1) to give the title compound as a white solid (0.495 g).
- 20

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.95 (m, 2H), 1.04-1.46 (m, 9H), 1.40 (s, 9H), 1.52-1.77 (m, 6H), 2.32 (m, 1H), 2.60 (m, 2H), 5.53 (br s, 1H), 5.78 (br s, 1H).

- 25 LRMS (ES) 3420 (M+Na).

#### PREPARATION 170'

TERT-BUTYL (3R)-3-CYANO-6-CYCLOHEXYLHEXANOATE



The title compound was obtained as a colourless oil from the compound of Preparation 169; using a similar method to that described in Preparation 159. The residue was purified by flash chromatography (graded elution of dichloromethane:hexane 1:4 to 1:0).

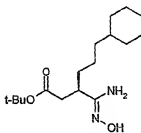
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-1.00 (m, 2H), 1.04-1.36 (m, 6H), 1.36-1.80 (m, 9H), 1.47 (s, 9H), 2.47 (dd, 1H), 2.60 (dd, 1H), 2.98 (m, 1H).

LRMS (TSP) 297 (M+Na).

[α]<sub>D</sub><sup>25</sup> = +12.6 ° (c = 1, MeOH)

#### PREPARATION 171'

TERT-BUTYL(3R)-3-[(E)-AMINO(HYDROXYIMINO)METHYL]-6-CYCLOHEXYLHEXANOATE



To a solution of the title compound from Preparation 170 (1.05 g, 5.9 mmol) in ethanol (60 mL) was added N-methylmorpholine (1.95 mL, 7.17 mmol), and hydroxylamine hydrochloride (1.23 g, 17.7 mmol). The reaction was stirred at reflux for 12 hours and then the solvent was removed in vacuo. The residue was diluted in ethyl acetate (150 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (graded elution of dichloromethane/ethyl acetate 4:1 to 2:1) to give the title compound as an oil (0.41 g).

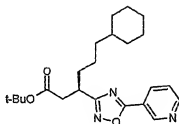
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.78-0.98 (m, 2H), 1.03-1.96 (m, 17H), 1.42 (s, 9H), 2.32-2.73 (m, 3H), 4.72 (s, 1H).

LRMS (ES) 313 (M+H).

5

#### PREPARATION 172

TERT-BUTYL (3R)-6-CYCLOHEXYL-3-[5-(3-PYRIDINYL)-1,2,4-OXADIAZOL-3-  
YL]HEXANOATE



10

To a solution of the title compound from Preparation 170' (0.410 g, 1.3 mmol) in dichloromethane (15 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.265 g, 1.38 mmol), 4-dimethylamino pyridine (0.016 g, 0.13 mmol), and nicotinic acid (0.170 g, 1.38 mmol) and the reaction was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate (30 mL) and water (30 mL). The layers were separated and aqueous layer extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient elution of dichloromethane /methanol 99:1 to 96:4), then dissolved in dichloromethane (5 mL) and heated at 140 °C for 1.5 hours. The solvent was removed in vacuo and residue purified by flash chromatography on silica gel (gradient elution of hexane/ethyl acetate 4:1 to 2:1), to give the title compound as a yellow oil (0.24 g).

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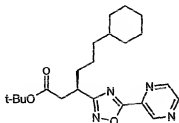
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<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-0.98 (m, 2H), 1.00-1.46 (m, 9H), 1.42 (s, 9H), 1.46-1.88 (m, 6H), 2.64 (m, 1H), 2.80 (m, 1H), 3.43 (m, 1H), 7.48 (m, 1H), 8.40 (m, 1H), 8.81 (1H), 9.37 (s, 1H).

LRMS (ES) 419 (M+NH<sub>4</sub>).

**PREPARATION 173**

TERT-BUTYL(3R)-6-CYCLOHEXYL-3-[5-(2-PYRAZINYL)-1,2,4-OXADIAZOL-3-YL]HEXANOATE



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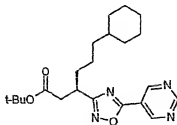
The title compound was obtained as a colourless oil from the compound of Preparation 171' and 2-pyrazinecarboxylic acid; using a similar method to that described in Preparation 172'. The residue was heated at 130 °C for 3 hours.

- 10 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.78-0.90 (m, 2H), 1.05-1.38 (m, 8H), 1.40 (s, 9H), 1.52-1.92 (m, 7H), 2.64 (dd, 1H), 2.80 (dd, 1H), 3.48 (m, 1H), 8.80 (s, 2H), 9.43 (s, 1H).

LRMS (TSP) 401 (M+H).

15 **PREPARATION 174**

TERT-BUTYL(3R)-6-CYCLOHEXYL-3-[5-(5-PYRIMIDINYL)-1,2,4-OXADIAZOL-3-YL]HEXANOATE



- 20 The title compound was obtained as a colourless oil from the compound of Preparation 171 and 5-pyrimidinecarboxylic acid; using a similar method to that described in Preparation 172. The residue was heated at 145 °C for 2.5 hours.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.76-0.92 (m, 2H), 1.05-1.46 (m, 8H), 1.41 (s, 9H), 1.53-1.86 (m, 7H), 2.64 (dd, 1H), 2.80 (dd, 1H), 3.45 (m, 1H), 9.42 (m, 3H).

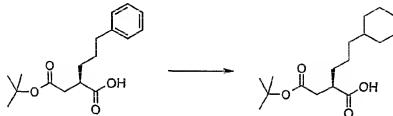
25

LRMS (ES) 423 (M+Na).

**Preparation 175: (2R)-2-[2-(tert-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid**

**Route A:**

(2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid



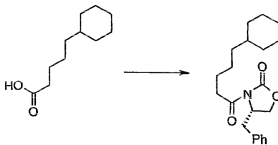
- 10 A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenylpentanoic acid (Syn. Lett.; 1998; 637-639) (10.00g, 34.2mmol) in acetic acid (120ml) was treated with 5% Rhodium on alumina catalyst, pressurised to 60psi with hydrogen in a sealed vessel and stirred at room temperature for 17 hours. The mixture was filtered through a pad of Arbocel<sup>®</sup> and the solvent was removed from the filtrate under reduced pressure. The residue was azeotroped from toluene to afford the
- 15 title compound (7.53g).

MS : 299 (MH<sup>+</sup>)

- <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.80 (1H, m), 2.61 (1H, m), 2.38 (1H, m), 1.75-1.56 (7H, m), 1.55-1.04 (17H, m), 0.84 (2H, m).
- 20

**Route B:**

(4S)-4-Benzyl-3-(5-cyclohexylpentanoyl)-1,3-oxazolidin-2-one



25

A solution of 5-cyclohexylpentanoic acid (63.50g, 345mmol) in N,N-dimethylformamide (0.5ml) and dichloromethane (350ml) was cooled to 5°C and treated dropwise with oxalyl chloride

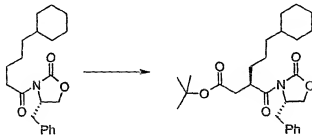
(31.6ml, 362mmol) over 30 minutes. The mixture was stirred at 0°C for 3 hours then the solvent was removed under reduced pressure to afford 5-cyclohexylpentanoyl chloride as a pale yellow solid (70.0g).

A solution of n-butyllithium (100ml, 250mmol, 2.5M in hexanes) was added via a cannula to a solution of (4S)-4-benzyl-1,3-oxazolidin-2-one (44.30g, 250mmol) in anhydrous tetrahydrofuran (400ml) at -78°C. The yellow solution was then stirred for 45 minutes. A solution of 5-cyclohexylpentanoyl chloride (55.5g, 275mmol) in tetrahydrofuran (100ml) was then added over 1 hour. The mixture was stirred at -78°C for 30 minutes then warmed to room temperature over 1 hour. The mixture was quenched with an aqueous solution of ammonium chloride (20% w/v, 400ml) and extracted with ethyl acetate. The layers were separated and the organic layer was washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The solid was recrystallised from hexane (500ml) to afford the title compound as a white solid (81.0g).

MS: 344 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 7.41-7.13 (5H, m), 4.68 (1H, m), 4.27-4.02 (2H, m), 3.31 (1H, dd, J=16, 4Hz), 3.06-2.70 (3H, m), 1.81-1.53 (7H, m), 1.49-1.04 (8H, m), 0.88 (2H, m)

tert-Butyl 3-[[[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl]-6-cyclohexylhexanoate



A solution of (4S)-4-benzyl-3-(5-cyclohexylpentanoyl)-1,3-oxazolidin-2-one (70.0g, 204mmol) in anhydrous tetrahydrofuran (650ml) was cooled to -70°C and treated dropwise with sodium hexamethyldisilazide (1M in tetrahydrofuran, 224ml, 224mmol) over 45 minutes. The mixture was stirred for a further 45 minutes before being treated with t-butylbromooacetate (31.6ml, 214mmol). This mixture was stirred at -70°C for 30 minutes then warmed to -30°C and quenched with an aqueous solution of ammonium chloride (20%w/v, 400ml) and warmed to room temperature. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over anhydrous sodium sulphate and the solvent removed under

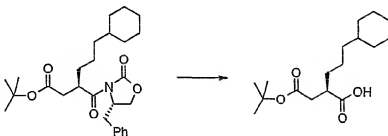


reduced pressure. The solid was recrystallised from hexane to afford the title compound as a white solid (71.4g).

MS: 458(MH<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 7.41-7.13 (5H, m), 4.66 (1H, m), 4.23-4.03 (3H, m), 3.35 (1H, dd, J=16, 4Hz), 2.95-2.68 (3H, m), 2.47 (1H, m), 1.80-1.07 (24H, m), 0.85 (2H, m)

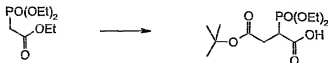
2-[2-(tert-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid



A solution of tert-butyl 3-[[[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl]-6-cyclohexylhexanoate (64.0g, 139.9mmol) in tetrahydrofuran : water (3:1, 800ml) was cooled to 5°C then treated sequentially with hydrogen peroxide (30%w/v water, 87ml, 769mmol) then lithium hydroxide hydrate (10.0g, 238mmol). The reaction was stirred for 1 hour then quenched by dropwise addition of an aqueous solution of sodium thiosulphate (500ml) keeping the temperature below 20°C. The mixture was extracted with ethyl acetate (discarded) and the aqueous phase was acidified to pH 2 with solid citric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (2 : 1) gradually changing to hexane : ethyl acetate (1 : 1) to afford the title compound (40.7g)

Route C:

3-(Diethoxyphosphoryl)succinic acid 1-tert-butyl ester



- Triethylphosphonoacetate (102g, 0.45 mol) was added dropwise over 11 min to a stirred solution of potassium *tert*-butoxide (60g, 0.54 mol) in THF (500ml), at 0°C, under nitrogen. The mixture was stirred for 1 hour at 0°C and then dichloromethane (300ml) was added and the reaction mixture was warmed to 25-30°C. The mixture was stirred at 25-30°C for 1 hour and then added dropwise over 33 minutes to a solution of *tert*-butyl bromoacetate (96g, 0.49 mol) in THF (500ml), at 0°C, under nitrogen. The mixture was stirred at 0-5°C for 2 hours and then a solution of citric acid (174g, 0.91 mol) in demineralised water (250ml) was added. The mixture was concentrated *in vacuo* to remove most of the THF and then toluene (750ml) was added. The organic phase was separated, washed with brine (2x150ml) and concentrated *in vacuo* to leave a colourless oil. The oil was taken up in ethanol and a solution of potassium hydroxide (36g, 0.64mol) in demineralised water (150ml) was added dropwise over 15 mins. The mixture was stirred at 0°C for 4 hours and then a solution of citric acid (158 g, 0.82 mol) in demineralised water (600ml), and toluene (600ml), were added. The organic phase was separated and the aqueous phase was re-extracted with toluene (600ml). The combined organic phases were washed with demineralised water (2x150ml) and concentrated *in vacuo* to leave a white solid. Toluene (150ml) was added and the slurry was re-concentrated *in vacuo* to leave a white solid. The product was purified by crystallisation from *tert*-butylmethyl ether (300ml) and cyclohexane (600ml) to give the title compound as a solid (79g).
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 4.20-4.10 (4H, m), 3.49-3.36 (1H, m), 3.00-2.85 (1H, m), 2.72-2.60 (1H, m), 1.20 (9H, s), 1.37-1.27 (6H, m)

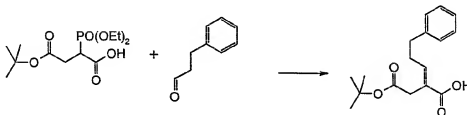
Alternative preparation:

- Triethylphosphonoacetate (12.0Kg, 53.5 mol) was added over 30 minutes to a stirred solution of potassium *tert*-butoxide (7.20Kg, 64.2 mol) in THF (118 litres), between 0 and 5°C, under nitrogen. The mixture was warmed to 25-30°C where it was stirred for 1 hour and then added over 45 minutes to a solution of *tert*-butyl bromoacetate (11.5Kg, 59.0 mol) in THF (28 litres), between 0 and 5°C, under nitrogen. The mixture was stirred at 0-5°C for 1 hour and then demineralised water (6.1 litres) and ethanol (30 litres) were added. A solution of potassium hydroxide (4.2Kg, 75.0 mol) in demineralised water (84 litres) was then added over 2 hours, between -5 and 0°C. The mixture was stirred at -10°C for 16 hours and then a solution of citric acid (16.5Kg, 85.8 mol) in demineralised water (32 litres) was added. The mixture was concentrated *in vacuo* to a volume of 180 litres and then ethyl acetate (90 litres) was added. The organic phase was separated and the aqueous phase was re-extracted with ethyl acetate (30 litres). The combined organic phases were washed with water (30 litres) and then stripped and replaced with cyclohexane by distillation at atmospheric pressure, at a constant volume of 72 litres. *tert*-Butylmethyl ether (18 litres) was added and the mixture was stirred at ambient

temperature for 12 hours and then filtered. The residue was washed with a mixture of cyclohexane (16 litres) and *tert*-butylmethyl ether (3.6 litres) then dried *in vacuo* for 16 hours to give the title compound as a colourless solid (10.0Kg, 60%).

- 5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 4.20-4.10 (4H, m), 3.49-3.36 (1H, m), 3.00-2.85 (1H, m), 2.72-2.60 (1H, m), 1.20 (9H, s), 1.37-1.27 (6H, m)

(E)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid



10

- A solution of 3-(diethoxyphosphoryl)succinic acid 1-*tert*-butyl ester (100g, 0.32mol) in THF (300ml) was added dropwise over 15 min to a stirred solution of potassium *tert*-butoxide (110g, 0.98mol) in THF (300ml), between -10 and -5°C, under nitrogen. The mixture was stirred at -10°C for 15 min and then a solution of hydrocinnamaldehyde (46.8g, 0.35mmol) in THF (100ml) was added dropwise over 15 min, between -13 and -8°C. The mixture was stirred at -10°C for 30 min and then a solution of citric acid (111g, 0.58mol) in demineralised water (500ml), and ethyl acetate (500ml), were added. The pH was adjusted to pH 4 with aqueous sodium hydroxide solution (50%) and the phases were separated. The aqueous fraction was washed with ethyl acetate (500ml) and the combined organic fractions were washed with saturated sodium bicarbonate solution (500ml), citric acid solution (10%, 500ml) and demineralised water (500ml) and then concentrated *in vacuo*. The resulting solid was slurried in cyclohexane (470ml) for 1 hour and then the mixture was filtered. The residue was washed with cyclohexane (2x50ml) and dried *in vacuo* to leave the title compound as a colourless solid (76g, 81%).

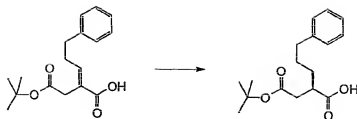
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MS : 289 [(M-H)]<sup>+</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 7.33-7.16 (5H, m), 7.05 (1H, br t), 3.20 (2H, s), 2.89 (2H, br t), 2.50 (2H, br dd), 1.41 (9H, s)

30

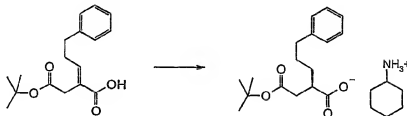
(R)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-phenylpentanoic acid



A stirred solution of (E)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid (100g, 0.34mol), cyclohexylamine (39ml, 0.34mol) and [(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]chloro(*p*-cymene)ruthenium chloride (0.64g, 0.69mmol) in methanol (1000ml) was heated to 60°C, under hydrogen (60p.s.i.), for 42 hours and then allowed to cool to room temperature. The mixture was filtered through celite and then concentrated in vacuo to a yellow solid which was purified by re-crystallisation from acetone (850ml). The resulting solid was partitioned between ethyl acetate (1200ml) and citric acid solution (10%, 1200ml) and the organic phase was separated, washed with demineralised water (1200ml) and concentrated in vacuo to leave the title compound as an oil (80g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 7.30-7.17 (5H, m), 2.85-2.78 (1H, m), 2.66-2.58 (3H, m), 2.37 (1H, br dd), 1.75-1.51 (4H, m), 1.40 (9H, s)

Preparation of cyclohexylamine salt:

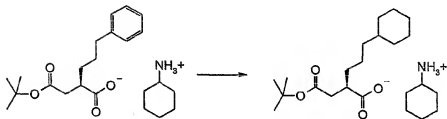


A stirred solution of cyclohexylamine (266ml, 2.32 mol), (E)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid (688g, 2.37 mol) and [(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]chloro(*p*-cymene)ruthenium chloride (4.4g, 4.7 mmol) in methanol (6.9 litres) was heated to 60°C, under hydrogen (60p.s.i.), for 47 hours and then allowed to cool to room temperature (enantiomeric excess= 88%). The mixture was filtered through celite and then the solvent was stripped and replaced with acetone by distillation at atmospheric pressure, at a constant volume of 4.2 litres. The resulting suspension was cooled to room temperature where it was stirred for 4 hours and then filtered. The residue was washed with acetone (2x 1 litre) and

then dried *in vacuo* at 45°C for 16 hours to leave the title compound as a colourless solid (590g, 64%, enantiomeric excess=98.9%).

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ : 7.23-7.09 (5H, m), 3.05-2.98 (1H, m), 2.64-2.56 (3H, m), 2.53 (1H, dd, *J* 15.2, 7.2Hz), 2.23 (1H, dd, *J* 15.2, 7.2Hz), 2.00-1.97, (2H, m), 1.85-1.81 (2H, m), 1.72-1.20 (10H, m), 1.40 (9H, s)

(R)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid cyclohexylamine salt



10

(R)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-phenylpentanoic acid cyclohexylamine salt (691g, 1.77 mol) and ethyl acetate (7.0 litres) were added to an aqueous solution of citric acid (10%, 6.3 litres) and the organic phase was separated, washed with water (7.0 litres) and concentrated *in vacuo* to a yellow oil. A solution of the oil and 5% rhodium on carbon (51.6g) in methanol (7.0 litres) was stirred at ambient temperature, under hydrogen (150p.s.i.) for 48 hours and then filtered through celite. To the filtrate was added cyclohexylamine (202ml, 1.77 mol) and the methanol solution was stripped and replaced with methylethyl ketone by distillation at atmospheric pressure, to a volume of 5.5 litres. The mixture was allowed to cool to ambient temperature where it was stirred for 48 hours and then filtered. The residue was washed with methylethyl ketone (2x 500ml) and then dried *in vacuo* at 45°C for 4 hours to leave the title compound as a colourless solid (495g, 71%).

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ : 3.06-2.99 (1H, m), 2.63-2.56 (1H, m), 2.53 (1H, dd, *J* 15.2, 7.2Hz), 2.23 (1H, dd, *J* 15.2, 7.2Hz), 2.02-1.97 (2H, m), 1.77-1.15 (21H, m), 1.43 (9H, s), 0.93-0.82 (2H, m)

25

(R)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid

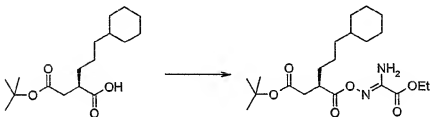


A solution of (R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenylpentanoic acid (2.2g, 7.5mmol) and 5%Rh/C (0.22g) in methanol (220ml) was stirred at room temperature, under hydrogen (150p.s.i.) for 24 hours and then filtered through celite. The filtrate was concentrated in vacuo to leave the title compound as an oil (2.0g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.82-2.76 (1H, m), 2.60 (1H, br dd), 2.37 (1H, br dd), 1.70-1.60 (6H, m), 1.51-1.30 (3H, m), 1.42 (9H, s), 1.23-1.11 (6H, m), 0.96-0.80 (2H, m)

#### Preparation 176

tert-Butyl (3R)-3-[((((Z)-1-amino-2-ethoxy-2-oxoethylidene)amino)oxy)carbonyl]-6-cyclohexylhexanoate



A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 175) (7.53g, 25.2mmol) in 1,4-dioxane (175ml) was treated with 1-hydroxybenzotriazole hydrate (3.75g, 27.8mmol) and the mixture cooled to 0°C. N,N'-Dicyclohexylcarbodiimide (5.47g, 26.5mmol) was then added and the mixture was stirred for 3 hours being allowed to warm to room temperature over this time. The mixture was then filtered and washed with 1,4-dioxane (2x50ml). The filtrate was then treated with sodium carbonate (4.01g, 37.8mmol) and ethyl 2-amino-2-(hydroxyimino)acetate (J.Org.Chem.;23; 1958; 1794) (3.33g, 25.2mmol). The resulting mixture was stirred at room temperature for 17 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate (x2). The combined organic

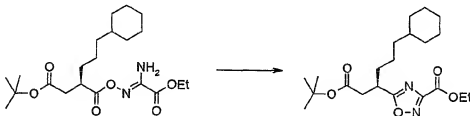
layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (30 : 70) gradually changing to ethyl acetate : pentane (50 : 50) to afford the title compound as a white solid (6.50g).

MS : 413 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 5.71 (2H, br s), 4.39 (2H, q), 2.92 (1H, m), 2.67 (1H, dd), 2.44 (1H, dd), 1.75-1.32 (22H, m), 1.26-1.04 (5H, m), 0.84 (2H, m).

#### Preparation 177

Ethyl 5-((1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl)-1,2,4-oxadiazole-3-carboxylate



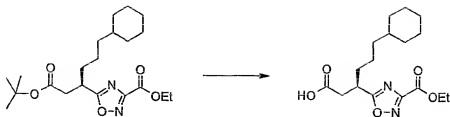
A solution of tert-Butyl (3R)-3-[[[[(Z)-1-amino-2-ethoxy-2-oxoethylidene]amino]oxy]carbonyl]-6-cyclohexylhexanoate (Preparation 176) (21.0g, 50.82mmol) in xylene (400ml) was heated at 130°C for 17 hours, then allowed to cool to room temperature. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (5 : 95) gradually changing to ethyl acetate : pentane (20 : 80) to afford the title compound as a colourless oil (20.0g).

MS : 395 (MH<sup>+</sup>), 412 (MNH<sub>4</sub><sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 4.51 (2H, m), 3.54 (1H, m), 2.86 (1H, dd), 2.65 (1H, dd), 1.86-1.57 (7H, m), 1.50-1.33 (12H, m), 1.30-1.03 (8H, m), 0.82 (2H, m).

#### Preparation 178

(3R)-6-Cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



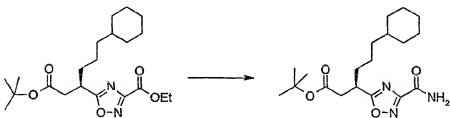
A solution of ethyl 5-((1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl)-1,2,4-oxadiazole-3-carboxylate (Preparation 177) (820mg, 2.08mmol) in dichloromethane (10ml) was cooled to 0°C and treated with trifluoroacetic acid (5ml). The mixture was stirred for 2.5 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue azeotroped with toluene (x2). The residue was then dissolved in ethyl acetate, washed sequentially with an aqueous solution of sodium dihydrogen citrate and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil (740mg).

MS : 339 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 4.49 (2H, q J=7Hz), 3.57 (1H, m), 3.05 (1H, dd J=17, 8Hz), 2.81 (1H, dd J=17, 4Hz), 1.92-1.55 (7H, m), 1.45 (3H, t J=7Hz), 1.35-1.02 (8H, m), 0.84 (2H, m)

#### Preparation 179

tert-Butyl (3R)-3-[3-(aminocarbonyl)-1,2,4-oxadiazol-5-yl]-6-phenylhexanoate



A solution of ethyl 5-((1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl)-1,2,4-oxadiazole-3-carboxylate (Preparation 178) (400mg, 1.01mmol) in ethanol saturated with ammonia gas (20ml) was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (90 : 10) gradually changing to hexane : ethyl acetate (60 : 40) to afford the title compound as a white solid (260mg).



MPt : 77-79°C

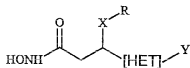
MS : 366 (MH<sup>+</sup>), 383 (MNa<sup>+</sup>)

- 5 Analysis : Found C, 62.42; H, 8.59; N, 11.48%;  $C_{19}H_{31}N_3O_8$  requires C, 62.44; H, 8.55; N, 11.50%

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.80 (1H, br s), 5.90 (1H, br s), 3.53 (1H, m), 2.87 (1H, dd, J=17, 9Hz), 2.66 (1H, dd, J=17, 5Hz), 1.90-1.50 (7H, m), 1.46-1.02 (17H, m), 0.83 (2H, m).

CLAIMS

1. A compound of formula (I):



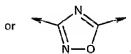
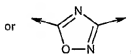
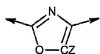
(I)

wherein:

X is C<sub>1-6</sub> alkylene or C<sub>2-6</sub> alkenylene, each of which is optionally substituted by one or more fluorine atoms;

R is aryl, C<sub>5-8</sub> cycloalkenyl or C<sub>3-8</sub> cycloalkyl optionally substituted by one or more fluorine atoms;

[HET] is a divalent heterocyclic moiety selected from



Z is H or C<sub>1-4</sub> alkyl,

Y is a mono- or bicyclic unsaturated ring system containing from 5 to 10 ring atoms, of which up to 4 which are hetero-atoms independently selected from N, O and S, and which ring system is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> or het<sup>1</sup>,

R<sup>1</sup> and R<sup>2</sup> are each independently selected from H and C<sub>1-4</sub> alkyl optionally substituted by C<sub>1-4</sub> alkoxy,

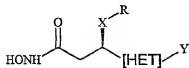
5     het<sup>1</sup> is a N-linked 4- to 6-membered mono- or bicyclic heterocycle optionally containing 1 or 2 further hetero ring atoms independently selected from N and O, which heterocycle is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> or het<sup>2</sup>,

10     het<sup>2</sup> is a N-linked 4- to 6-membered mono- or bicyclic heterocycle optionally containing 1 or 2 further hetero ring atoms independently selected from N and O,

"aryl" is phenyl optionally substituted by one or more substituents independently selected from R<sup>3</sup>, OH, SO<sub>2</sub>(C<sub>1-4</sub> alkyl) and/or C(O)<sub>p</sub>(C<sub>1-4</sub> alkyl) groups,

15     and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

2. A compound according to claim 1 which has the stereochemistry of formula (IA):



(IA)

20     and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

3. A compound according to claim 1 or claim 2 wherein X is a linear C<sub>2-6</sub> alkylene moiety optionally substituted by one or more fluorine atoms, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

25

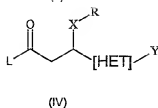
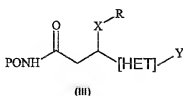
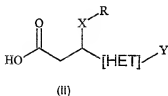
4. A compound according to claim 3 wherein X is propylene, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof..

5. A compound according to any one of claims 1 to 4 wherein R is C<sub>3-6</sub> cycloalkyl optionally substituted by one or more fluorine atoms, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

30

6. A compound according to claim 5 wherein R is cyclobutyl, cyclopentyl or cyclohexyl optionally substituted by one or more fluorine atoms, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
- 5 7. A compound according to claim 6 wherein R is cyclohexyl, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
8. A compound according to any one of claims 1 to 7 wherein Y is a 5- or 6-membered unsaturated ring containing 0, 1 or 2 ring hetero-atoms independently selected from N and O, and which ring is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> and het<sup>1</sup>, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
- 10 and which ring is optionally substituted by one or more substituents independently selected from =O, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, NR<sup>1</sup>R<sup>2</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, CO<sub>2</sub>R<sup>1</sup>, CONR<sup>1</sup>R<sup>2</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>CO<sub>2</sub>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup> and het<sup>1</sup>, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
- 15 9. A compound according to claim 8 wherein Y is a 5- or 6-membered unsaturated ring containing 0, 1 or 2 ring hetero-atoms independently selected from N and O, and which ring is optionally substituted by one or more substituents independently selected from =O, CONH<sub>2</sub>, CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, CH<sub>3</sub>, NH<sub>2</sub>, CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, CO<sub>2</sub>H, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, NHCH<sub>3</sub>, NHC<sub>2</sub>H<sub>5</sub>, N(CH<sub>3</sub>)<sub>2</sub>, morpholino, imidazol-1-yl, methoxy, ethoxy and NHSO<sub>2</sub>CH<sub>3</sub>, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
- 20 acceptable salts, solvates (including hydrates) and prodrugs thereof.
10. A compound according to claim 9 wherein Y is 5-carbamoylpyridin-3-yl, uracil-5-yl, pyridin-4-yl, 6-methylpyridin-3-yl, 5-carboxypyridin-3-yl, 6-methoxycarbonylmethylpyridin-3-yl, 6-(4-methylpiperazino)pyridin-3-yl, 6-(3-dimethylaminoazetidino)pyridin-3-yl, 6-(3-morpholinoazetidino)pyridin-3-yl, 4-carboxypyridin-2-yl, 6-dimethylaminopyridin-3-yl, 6-(imidazol-1-yl)pyrazin-2-yl, 3-morpholinopyrazin-2-yl, 3-pyrrolidinopyrazin-2-yl, 3-dimethylaminopyrazin-2-yl, 3-methylaminopyrazin-2-yl, 3-methylsulphonamidophenyl, 3-carboxyphenyl or 6-ethoxypyrazin-2-yl, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
- 25 morpholinopyrazin-2-yl, 3-methylaminopyrazin-2-yl, 3-methylsulphonamidophenyl, 3-carboxyphenyl or 6-ethoxypyrazin-2-yl, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
- 30 11. A compound according to claim 10 wherein Y is uracil-5-yl or 4-carboxypyridin-2-yl, and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.
12. A compound according to any one of claims 1 to 11 wherein [HET] is 1,2,4-oxadiazol-3,5-ylene, and the salts, solvates and prodrugs thereof.
- 35 ylene, and the salts, solvates and prodrugs thereof.

13. A compound of formula (I) according to claim 1 wherein each substituent is as specified in the Examples, and the salts, solvates and prodrugs thereof.
14. A compound according to claim 1 which is selected from any one of the Examples described herein, and the salts, solvates and prodrugs thereof.
15. A compound, salt solvate or prodrug according to any one of claims 1 to 14 for use in medicine.
- 10 16. A compound, salt, solvate or prodrug according to any one of claims 1 to 14 for use in a medicament for the treatment of a PCP-mediated condition.
17. The use of a compound, salt, solvate or prodrug according to any one of claims 1 to 14 in the manufacture of a medicament useful for treating a PCP mediated condition and/or disease, such as an antiscarring medicament.
- 15 18. A pharmaceutical composition comprising a compound, salt, solvate or prodrug according to any one of claims 1 to 14 and a pharmaceutically acceptable adjuvant, diluent or excipient.
- 20 19. A method of treating a PCP-mediated condition or disease, such as scar tissue, in a patient comprising administering to said patient a therapeutically effective amount of a compound, salt, solvate or prodrug according to any one of claims 1 to 14.
- 25 20. A process to make a compound according to claim 1, wherein the substituents are as defined herein, which comprises one or more of the following steps:



(a) deprotecting a compound of formula (III) where P is a NHO-protecting group:

(b) reaction of a compound of formula (II) with hydroxylamine, optionally first reacting the acid (II) with a coupling agent;

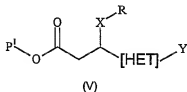
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(c) reaction of a an activated acid derivative (IV), where L is a suitable leaving group, with a protected hydroxylamine species "PONH<sub>2</sub>", to give compounds of formula (iii), above;

(d) reaction of a compound of formula (IV) with hydroxylamine;

10 and/or

(e) deprotection of a compound of formula (V) wherein P1 is a suitable carboxylic acid protecting group



15 to give a compound of formula (II) above.

21. A compound of formula (II), (III), (IV) or (V) according to claim 20.

## INTERNATIONAL SEARCH REPORT

 Intern Application No  
 PCT/IB 02/00699

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07D413/04 C07D271/08 C07D413/14 C07D271/06 C07D263/32 A61K31/496 A61P17/02		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPC-Internal		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 58278 A (NATANABE FUMIHIKO ; SHIONOGI & CO (JP); ARAKI YOSHITAKA (JP); HARA) 5 October 2000 (2000-10-05) the whole document	1-21
A	WO 99 29667 A (WHITLOCK GAVIN ALISTAIR ; DACK KEVIN NEIL (GB); PFIZER LTD (GB); PF) 17 June 1999 (1999-06-17) the whole document	1-21
P,X	WO 01 47901 A (BILLOTTE STEPHANE ; FISH PAUL VINCENT (GB); THOMSON NICHOLAS MURRAY) 5 July 2001 (2001-07-05) cited in the application the whole document	1-21
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *Z* document member of the same patent family		
Date of the actual completion of the international search 17 June 2002		Date of mailing of the international search report 27/06/2002
Name and mailing address of the ISA European Patent Office, P.B. 5618 Palensteinlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Grassi, D

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

Inter- application No  
PCT/IB 02/00699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0058278 A	05-10-2000	AU 3196200 A WO 0058278 A1	16-10-2000 05-10-2000
WO 9929667 A	17-06-1999	AP 930 A AU 741859 B2 AU 1230199 A BG 104506 A BR 9813360 A CA 2312935 A1 CN 1281433 T CZ 20002037 A3 WO 9929667 A1 EP 1036062 A1 HR 20000373 A1 HU 0100845 A2 JP 2001525396 T NO 20002826 A NZ 504421 A PL 341031 A1 SK 7822000 A3 TR 200001611 T2 US 6387931 B1 ZA 9811112 A	26-01-2001 13-12-2001 28-06-1999 31-01-2001 17-10-2000 17-06-1999 24-01-2001 12-09-2001 17-06-1999 20-09-2000 31-12-2000 28-08-2001 11-12-2001 26-07-2000 01-02-2002 26-03-2001 03-12-2001 23-10-2000 14-05-2002 05-06-2000
WO 0147901 A	05-07-2001	AU 1875601 A WO 0147901 A1 US 2001021718 A1	09-07-2001 05-07-2001 13-09-2001



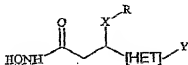
## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 02/00699

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Compounds of compounds of formula (I):



(I)

and their salts, solvates and prodrugs, wherein the substituents are as defined herein, are Procollagen C-proteinase inhibitors for the treatment of scars.